NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF DIVINYLBENZENE-HP

(CAS NO. 1321-74-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

Scheduled Peer Review Date: September 27-28, 2005

<u>NOTICE</u>

This DRAFT Technical Report is distributed solely for the purpose of predissemination peer review under applicable information quality guidelines. It has not been formally disseminated by the NTP. It does not represent and should not be construed to represent NTP determination or policy.

NTP TR 534

NIH Publication No. 05-4470

National Toxicology Program

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Details about ongoing and completed NTP studies, abstracts of all NTP Technical Reports, and full versions of the the completed reports are available at the NTP's World Wide Web site: http://ntp.niehs.nih.gov. In addition, printed copies of these reports are available from the NTP as supplies last (919-541-1371).

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National Institutes of Health

CONTRIBUTORS

National Toxicology Program
Evaluated and interpreted results and reported findings

D.L. Morgan, Ph.D., Study Scientist
G. Pearse, B.V.M.&S., Study Pathologist
D.W. Bristol, Ph.D.
J.R. Bucher, Ph.D.
R.S. Chhabra, Ph.D.
J.R. Hailey, D.V.M.
R.A. Herbert, D.V.M., Ph.D.
G.E. Kissling, Ph.D.
D.E. Malarkey, D.V.M., Ph.D.
R.R. Maronpot, D.V.M.
S.D. Peddada, Ph.D.
J.H. Roycroft, Ph.D.
C.S. Smith, Ph.D.
G.S. Travlos, D.V.M.
K.L. Witt, M.S.

Battelle Northwest Operations
Conducted studies and evaluated pathology findings

J.A. Dill, Ph.D., Principal Investigator (2-year studies)
S.L. Grumbein, D.V.M., Ph.D.
R.A. Renne, D.V.M.
B.K. Hayden

Experimental Pathology Laboratories, Inc.
Provided pathology review

M.H. Hamlin, II, D.V.M., Principal Investigator
P. Howroyd, M.A., VetMB
J.C. Peckham, D.V.M., M.S., Ph.D.

Dynamac Corporation
Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

NTP Pathology Working Group
Evaluated slides and prepared pathology report on rats (July 17, 2003)

W.G. Lieuallen, D.V.M., Ph.D., Chairperson
Pathology Associates, A Charles River Company
M.T. Butt, D.V.M.
Pathology Associates, A Charles River Company
J.T. Boyce, D.V.M., Ph.D., Observer
Pathology Associates, A Charles River Company
S. Harbo, D.V.M., Observer
Battelle Northwest Operations
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
P. Howroyd, M.A., VetMB
Experimental Pathology Laboratories, Inc.
D.E. Malarkey, D.V.M., Ph.D.
National Toxicology Program
G. Pearse, B.V.M.&S.
National Toxicology Program
J.C. Peckham, D.V.M., M.S., Ph.D.
Experimental Pathology Laboratories, Inc.
R.C. Sills, D.V.M., Ph.D.
National Toxicology Program

Evaluated slides and prepared pathology report on mice (March 6, 2003)

W.G. Lieuallen, D.V.M, Ph.D., Chairperson
Pathology Associates, A Charles River Company
M.T. Butt, D.V.M.
Pathology Associates, A Charles River Company
D. Dixon, D.V.M., Ph.D.
National Toxicology Program
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
G. Pearse, B.V.M.&S.
National Toxicology Program
J.C. Peckham, D.V.M., M.S., Ph.D.
Experimental Pathology Laboratories, Inc.

Constella Group, Inc.
Provided statistical analyses

P.W. Crockett, Principal Investigator
L.J. Betz, M.S.
M.R Easterling, Ph.D.
K.P. McGowan, M.B.A.
J. Matthews, M.S.

Biotechnical Services, Inc.
Prepared Technical Report

S.R. Gunnels, M.A., Principal Investigator
N.N. Buchanan, B.S.
L.M. Harper, B.S.
J.I. Powers, M.A.P.
D.C. Serbus, Ph.D.

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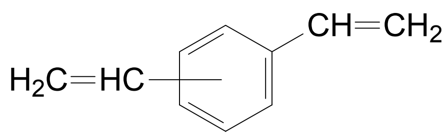
ABSTRACT



DIVINYLBENZENE-HP

CAS No. 1321-74-0

Chemical Formula: $C_{10}H_{10}$ Molecular Weight: 130.189

Synonyms: Benzene, diethenyl-(9CI); diethenylbenzene; divinyl benzene; divinylbenzene-HP (high purity); divinylbenzene (*m*-and *p*-mixture); divinylbenzene (*m*-, *p*-mixture); divinyl benzene, mixed isomers; DVB; DVB- *m*- (or *p*-) divinylbenzene; vinylstyrene

Divinylbenzene-HP is used for producing vinyl polymers. Divinylbenzene-HP was nominated for study by the National Cancer Institute because of the potential for worker exposure and the structural similarity of divinylbenzene to styrene, a potential human carcinogen. Male and female F344/N rats and B6C3F$_1$ mice were exposed to divinylbenzene-HP (80%) by inhalation for 2 weeks, 3 months, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and mouse peripheral blood erythrocytes.

2-Week Study in Rats

Groups of five male and five female rats were exposed by whole body inhalation to divinylbenzene-HP at target concentrations of 0, 25, 50, 100, 200, or 400 ppm 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 16 days. All rats survived to the end of the study. Statistically significant decreases in group mean body weights occurred in both male and female rats in the 400 ppm group. Relative kidney weights of 50 ppm or greater males

and relative liver weights of 200 and 400 ppm males were significantly greater than those of the chamber controls. A clear serous nasal/eye discharge was observed in groups of rats exposed to 100 ppm or greater. Minimal or mild rhinitis occurred in 400 ppm rats of both sexes.

2-Week Study in Mice

Groups of five male and five female mice were exposed by whole body inhalation to divinylbenzene-HP at target concentrations of 0, 25, 50, 100, 200, or 400 ppm for 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 17 days. All 400 ppm males and females died on or before the second day of the study, and two male and two female 200 ppm mice died early. Final mean body weights and body weight gains of 100 and 200 ppm males were significantly less than those of the chamber controls. Thymus weights of exposed groups of males were significantly less than those of the chamber controls, and relative liver weights of 100 and 200 ppm males were significantly increased. Kidney and liver weights of exposed groups of females were significantly greater than those of the chamber controls. Mice exposed to 400 and 200 ppm had liver lesions including degeneration, necrosis, hemorrhage or cytomegaly. Renal tubule necrosis and regeneration occurred at 200 ppm. Necrosis or metaplasia of nasal epithelium and glands occurred in the nose in all exposure groups.

3-Month Study in Rats

Groups of 10 male and 10 female rats were exposed to divinylbenzene-HP at concentrations of 0, 25, 50, 100, 200, or 400 ppm for 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 14 weeks. All rats survived to the end of the study. There were no biologically significant changes in body weight in either sex. Nasal/eye discharge was occasionally noted in groups exposed to 50 ppm or greater. Kidney and liver weights of exposed groups of males and of 400 ppm females were generally greater than those of the chamber controls. In addition, the relative weights of the heart and testis were significantly increased in 200 and 400 ppm males. Incidences of degeneration of the olfactory epithelium in 200 and 400 ppm rats and basal cell hyperplasia of the olfactory epithelium in rats exposed to 100 ppm or greater were significantly increased.

3-Month Study in Mice

Groups of 10 male and 10 female mice were exposed to divinylbenzene-HP at concentrations of 0, 12.5, 25, 50, 100, or 200 ppm for 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 14 weeks. All 200 ppm males and nine 200 ppm females died early. Final mean body weights were significantly lower in males and females exposed to 25, 50, or 100 ppm when compared with chamber controls. Lethargy or hypoactivity was observed in the higher exposure concentration groups. Differences in organ weights were attributed to decreased body weights. Exposure to divinylbenzene was associated with necrosis of the liver and kidney of 200 ppm males and females dying early. In all exposed groups of male and female mice there was necrosis of nasal cavity lateral walls, olfactory epithelium, and glands with resultant atrophy of olfactory epithelium and glands in females. A lower number of animals had necrotic or degenerative changes of the upper respiratory tract.

2-Year Study in Rats

Groups of 50 male and 50 female rats were exposed to divinylbenzene-HP at concentrations of 0, 100, 200, or 400 ppm for 6 hours plus T_{90} (12 minutes) per day, 5 days per week for up to 105 weeks. Survival of 400 ppm females was significantly less than that of the chamber control group. Survival of all exposed groups of males was similar to that of the chamber control group. Mean body weights of 400 ppm males and females were significantly less than those of the controls during the second half of the study.

Renal tubule carcinomas occurred in two of 50 males exposed to 400 ppm in the original kidney sections; an incidence that exceeded the historical control range. In 400 ppm males, the incidence of renal tubule hyperplasia was increased, and the incidence of nephropathy was significantly increased. Following combined analysis of single and step section data, the incidences of renal tubule adenoma and adenoma or carcinoma (combined) were marginally higher in 200 and 400 ppm males, and the incidence of renal tubule hyperplasia was significantly increased in 400 ppm males. The incidence of basal cell adenoma of the skin was slightly increased in 400 ppm males and exceeded the historical range in chamber controls. The incidences of malignant glial cell tumors (malignant astrocytoma and oligodendroglioma) in the brain were slightly increased in 100 and 200 ppm males, and the incidence in the 200 ppm group exceeded the historical range for chamber controls. There were increased incidences of degenerative and regenerative changes in the olfactory epithelium in the nose of all exposed groups of rats. The incidence of focal chronic inflammation in the lung of 400 ppm males was significantly greater than in the chamber control group.

2-Year Study in Mice

Groups of 50 male and 50 female mice were exposed to divinylbenzene-HP at concentrations of 0, 10, 30, or 100 ppm for 6 hours plus T_{90} (12 minutes) per day, 5 days per week for up to 105 weeks. Survival of all exposed groups of male and female mice was similar to that of the chamber controls. Group mean body weights were lower relative to controls in 100 ppm males and in 30 and 100 ppm females.

The incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) in 100 ppm males were higher than chamber control incidences, but the incidences of adenoma or carcinoma (combined) were within the historical control range. The incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) in all exposed groups of females were generally greater than those of the chamber controls; the incidences were at the upper end or exceeded the historical control ranges. There was a greater incidence and severity of alveolar epithelial hyperplasia in 100 ppm females, and a greater severity of this lesion in 30 ppm females, when compared to chamber controls. The incidences and/or severity of atypical bronchiole hyperplasia were significantly increased in all exposed groups of mice. Nonneoplastic nasal lesions occurred in most exposed mice.

Genetic Toxicology

Divinylbenzene-HP was not mutagenic in any of three independent gene mutation assays using *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537 or *Escherichia coli* tester strain WPM uvrA with or without induced hamster or rat liver enzymes. No increases in the frequencies of micronucleated normochromatic erythrocytes or alterations in the percentages of polychromatic erythrocytes were seen in peripheral blood of male or female $B6C3F_1$ mice exposed to divinylbenzene-HP by inhalation for 3 months.

CONCLUSIONS

Under the conditions of this 2-year inhalation study, there was *equivocal evidence of carcinogenic activity** of divinylbenzene-HP in male F344/N rats based upon the occurrence of carcinomas in the kidney and glial tumors in the brain. There was *no evidence of carcinogenic activity* in female F344/N rats exposed to 100, 200, or 400 ppm divinylbenzene-HP. There was *no evidence of carcinogenic activity* in male $B6C3F_1$ mice exposed to 10, 30, or 100 ppm divinylbenzene-HP. There was *equivocal evidence of carcinogenic activity* of divinylbenzene-HP in female $B6C3F_1$ mice based on the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in the lung.

Exposure to divinylbenzene-HP caused nonneoplastic lesions in the nasal cavity of male and female rats including degeneration of the olfactory epithelium and basal cell epithelial hyperplasia. Nonneoplastic lesions were observed in the lung and nasal cavity of exposed mice. Atypical bronchiolar hyperplasia and hyperplasia of the alveolar epithelium were observed in lung of male and female mice. In the nasal cavity of mice, suppurative inflammation, metaplasia of the respiratory and olfactory epithelium, and degeneration of the olfactory epithelium were present at all concentrations.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Divinylbenzene-HP

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in air	Chamber control, 100, 200, or 400 ppm	Chamber control, 100, 200, or 400 ppm	Chamber control, 10, 30, or 100 ppm	Chamber control, 10, 30, or 100 ppm
Body weights	400 ppm group less than chamber control group	400 ppm group less than chamber control group	100 ppm group less than chamber control group	30 and 100 ppm groups less than chamber control group
Survival rates	Exposed groups similar to chamber control group	400 ppm group less than chamber control group	Exposed groups similar to chamber control group	Exposed groups similar to chamber control group
Nonneoplastic effects	Nose: olfactory epithelium, degeneration (0/50, 47/48, 49/50, 49/49); olfactory epithelium, hyperplasia, basal cell (0/50, 21/48, 44/50, 48/49); glands, dilatation (3/50, 30/48, 48/50, 46/49); goblet cell, hyperplasia (1/50, 3/48, 7/50, 16/49)	Nose: olfactory epithelium, degeneration (0/50, 50/50, 49/49, 48/49); olfactory epithelium, hyperplasia, basal cell (0/50, 25/50, 42/49, 48/49)	Lung: bronchiole, hyperplasia, atypical (0/49, 38/49, 46/49, 46/49); alveolar epithelium, hyperplasia (0/49, 5/49, 5/49, 7/49) Nose: inflammation, suppurative (3/50, 47/50, 49/49, 49/50); glands, respiratory epithelium, metaplasia (12/50, 50/50, 49/49, 50/50); olfactory epithelium, respiratory epithelium, metaplasia (1/50, 50/50, 49/49, 50/50); olfactory epithelium, degeneration, hyaline (5/50, 50/50, 48/49, 11/50)	Lung: bronchiole, hyperplasia, atypical (0/50, 39/50, 45/50, 48/49); alveolar epithelium, hyperplasia (4/50, 3/50, 4/50, 8/49) Nose: inflammation, suppurative (1/50, 50/50, 49/50, 49/49); glands, respiratory epithelium, metaplasia (3/50, 50/50, 50/50, 49/49); olfactory epithelium, respiratory epithelium, metaplasia (0/50, 50/50, 50/50, 49/49); olfactory epithelium, degeneration, hyaline (2/50, 50/50, 40/50, 8/49)
Neoplastic effects	None	None	None	None
Equivocal findings	Kidney: renal tubule carcinoma (standard evaluation - 0/50, 0/49, 0/50, 2/49); renal tubule adenoma or carcinoma (combined) (standard and extended evaluations - 0/50, 0/49, 2/50, 3/49) Brain: oligodendroglioma or astrocytoma (0/49, 1/50, 3/50, 0/50)	None	None	Lung: alveolar/bronchiolar adenoma or carcinoma (6/50, 12/50, 8/50, 13/49)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Divinylbenzene-HP

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Levels of evidence of carcinogenic activity	Equivocal evidence	No evidence	No evidence	Equivocal evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:		Negative in strains TA97, TA98, TA100, TA1535, and TA1537 and *Escheria coli* WPM uvrA with and without S9		
Micronucleated erythrocytes Mouse peripheral blood *in vivo:*		Negative in both males and females		

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results **(clear evidence and some evidence);** one category for uncertain findings **(equivocal evidence);** one category for no observable effects **(no evidence);** and one category for experiments that cannot be evaluated because of major flaws **(inadequate study).** These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

For studies showing multiple chemical-related neoplastic effects that if considered individually would be assigned to different levels of evidence categories, the following convention has been adopted to convey completely the study results. In a study with clear evidence of carcinogenic activity at some tissue sites, other responses that alone might be deemed some evidence are indicated as "were also related" to chemical exposure. In studies with clear or some evidence of carcinogenic activity, other responses that alone might be termed equivocal evidence are indicated as "may have been" related to chemical exposure.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from pre-neoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on divinylbenzene-HP on September 27-28, 2005, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

Charlene A. McQueen, Ph.D., Chairperson
College of Pharmacy
University of Arizona
Tucson, AZ

Diane F. Birt, Ph.D.
Department of Food Science & Human Nutrition
Iowa State University
Ames, IA

Michael R. Elwell, D.V.M., Ph.D.
Pathology, Drug Safety Evaluation
Pfizer Global Research and Development
Groton, CT

Thomas A. Gasiewicz, Ph.D.
Department of Environmental Medicine
Environmental Health Sciences Center
University of Rochester School of Medicine
Rochester, NY

John P. Giesy, Jr., Ph.D.
Department of Zoology
Michigan State University
East Lansing, MI

Shuk-Mei Ho, Ph.D.
Department of Surgery, Division of Urology
University of Massachusetts Medical School
Worcester, MA

Stephen M. Roberts, Ph.D.
Center for Environmental & Human Toxicology
University of Florida
Gainesville, FL

Mary Vore, Ph.D.
Graduate Center for Toxicology
University of Kentucky
Lexington, KY

Special Ad Hoc Reviewers

Kenny Crump, Ph.D.
Environ International
Ruston, LA

Prescott Deininger, Ph.D.
Tulane University Medical Center
New Orleans, LA

Harish Sikka, Ph.D.
Environmental Toxicology and Chemistry Laboratory
State University of New York College at Buffalo
Buffalo, NY

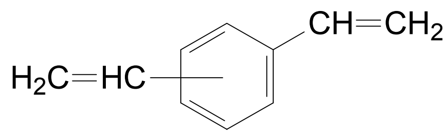
Keith Soper, Ph.D.
Merck Research Laboratories
West Point, PA

Vernon Walker, Ph.D.
Lovelace Respiratory Institute
Albuquerque, NM

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

NOTE: A summary of the Technical Reports Review Subcommittee's remarks will appear in a future draft of this report.

INTRODUCTION



DIVINYLBENZENE-HP

CAS No. 1321-74-0

Chemical Formula: $C_{10}H_{10}$ Molecular Weight: 130.189

Synonyms: Benzene, diethenyl-(9CI); diethenylbenzene; divinyl benzene; divinylbenzene-HP (high purity); divinylbenzene (*m*- and *p*-mixture); divinylbenzene (*m*-, *p*-mixture); divinyl benzene, mixed isomers; DVB; DVB-HP; *m*- (or *p*-) divinylbenzene; vinylstyrene

Chemical and Physical Properties

Divinylbenzene exists as *o*-, *m*-, and *p*-isomers; the commercial forms contain *m*- and *p*-divinylbenzenes, ethylvinylbenzenes, and diethylbenzenes (HSDB, 2005). The commercial grade containing 55% divinylbenzene is a pale, straw-colored liquid with a boiling point of 195° C and a density of 0.918 at 25° C. It is insoluble in water and soluble in methanol and ether. Because it is an explosion risk, it contains an inhibitor.

Production, Use, and Human Exposure

Divinylbenzene is a specialty monomer used primarily to make cross-linked polystyrene resins (*Kirk-Othmer*, 1983). Divinylbenzene monomer is manufactured by dehydrogenation of mixed isomeric diethylbenzenes (Figure 1). After removal of light by-products, the product is recovered as a mixture of *m*- and *p*-divinylbenzene and *m*- and *p*-ethylvinylbenzene, the partial dehydrogenation product. *o*-Diethylbenzene in the starting material is converted to naphthalene. Because the divinylbenzene monomer readily polymerizes to a brittle

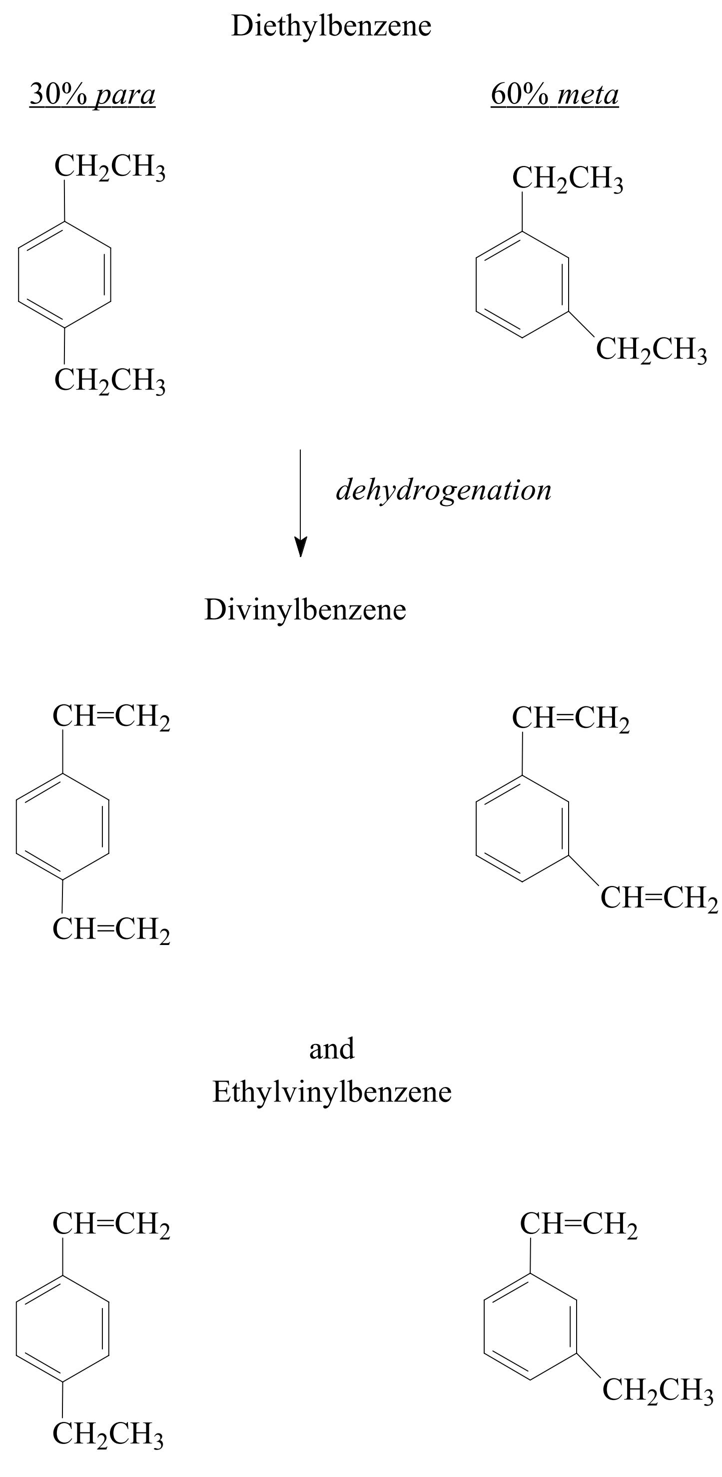


FIGURE 1
Dehydrogenation of Diethylbenzene to Divinylbenzene Monomer

insoluble resin, it is heavily inhibited with *tert*-butyl catechol and diluted with ethylvinylbenzene to minimize this reaction. Three commercial grades of divinylbenzene are produced containing approximately 22% (DVB-22), 55% (DVB-55), and 80% (DVB-HP) divinylbenzene (Table 1). Divinylbenzene-HP was the highest purity grade commercially available (80%) and was used in the studies presented in this Technical Report.

By far, the greatest use of divinylbenzene is as a cross-linking monomer for copolymerization with styrene or with acrylic and methacrylic acids to produce ion-exchange resins used in water treatment and in the chemical and pharmaceutical industries (Coulter and Kehde, 1970; *Kirk-Othmer*, 1981; 1983). Copolymerization with styrene results in resins with reduced solubility in most solvents, increased heat-distortion temperatures, increased surface hardness, and improved impact and tensile strengths (*Kirk-Othmer*, 1983). Divinylbenzene is also used in styrene-butadiene rubber to improve the swelling, shrinkage, and extrusion properties of the product (*Kirk-Othmer*, 1983). The divinylbenzene monomer has been used as a sustained release agent, as a dental filling component, and as an insecticide stabilizer (*Patty's*, 1981).

Occupational exposure to divinylbenzene occurs primarily by inhalation and dermal contact, consequently, divinylbenzene is an irritant to the eyes and respiratory system (*Patty's*, 1981). The current Occupational Safety and Health Administration threshold limit value (8-hour time-weighted average) for divinylbenzene is 10 ppm (ACGIH, 2004).

Table 1
Composition of Divinylbenzene Commercial Grades

	DVB-22	**DVB-55**	**DVB-80 (HP)**
Divinylbenzene (%)			
meta	17.1	36.4	60.3
para	8.2	18.6	21.6
Ethylvinylbenzene (%)			
meta	23.1	25.0	6.7
para	10.0	13.0	6.8
Inhibitors (ppm)			
tert-Butylcatechol	1,000	1,000	1,200-1,500
Sulfur	20	230	240

Absorption, Distribution, Metabolism, and Excretion

Experimental Animals

Divinylbenzene is structurally similar to styrene and is likely biotransformed by the same metabolic pathways. Styrene is metabolized in animals and humans by cytochrome P450 to styrene-7,8-epoxide, a direct-acting carcinogen (IARC, 1987), and because divinylbenzene is likely oxidized to a similar epoxide or diepoxide, there is concern about the potential carcinogenicity of this chemical. Because divinylbenzene has two reactive vinyl groups, it may be metabolized to a toxic epoxide more readily than styrene. In addition, commercial formulations of divinylbenzene contain a significant amount of ethylvinylbenzene that could also be metabolized to a reactive epoxide.

An ADME study of [^{14}C] *m*-divinylbenzene in male F344 rats with oral exposures of 40, 200, and 1,200 mg/kg and an intravenous dose of 40 g/kg has been reported (Jeffcoat *et al*., 1990). The majority of the [^{14}C] *m*-divinylbenzene-derived radioactivity was excreted in urine. The amount excreted in urine increased as the oral dose increased, 72% for 40 mg/kg to 89% for 1,200 mg/kg. Excretion in urine following intravenous dosing was 82%, approximately the same as from oral administration, indicating nearly complete absorption of the oral exposures. The authors speculated that excretion in bile was saturated at the high exposure, leading to a greater percentage of the dose in urine. A repeated dose study did not lead to accumulation of [^{14}C] *m*-divinylbenzene-derived radioactivity in tissue and indicated induction of metabolism. HPLC analysis of urine indicated the presence of at least 12 metabolites. The major metabolite was identified as the mono-glucuronide of 3-(ethenylphenyl) ethanediol.

The metabolism of each of the 3 isomers of divinylbenzene in Wistar rats has been reported by Linhart *et al*. (1989, 1992, 1996). A composite of their findings is presented in Figure 2. The identification of metabolites included acid/base extraction, column chromatography on silica gel, treatment with diazomethane and analysis by gas chromatography-mass spectrometry.

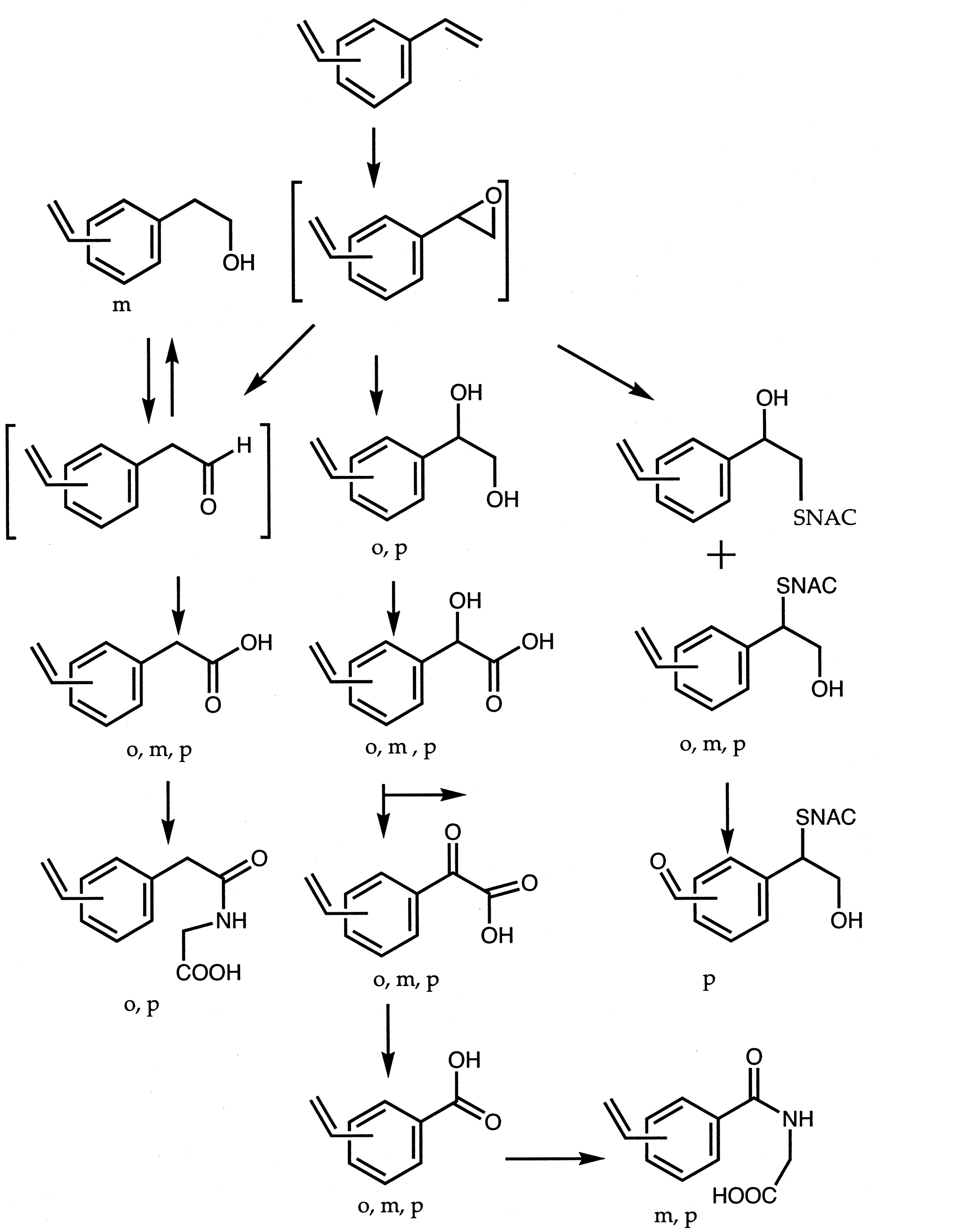


FIGURE 2
Metabolic Pathway for Divinylbenzenes
Brackets indicate reactive intermediates not directly identified. Those metabolites identified in urine of Wistar rats treated with *ortho*-divinylbenzene are labeled [o], likewise [m] for *meta*- and [p] for *para*-divinylbenzene.

Humans

An *in vitro* study comparing metabolism of *m*-divinylbenzene in liver slices from rats, mice, and humans determined that epoxidation, hydrolysis of the epoxide, and glucuronidation of the resulting diol was the main metabolic pathway in all three species. Both monoglucuronides of the diol were identified (Jeffcoat, 1999).

TOXICITY

Experimental Animals

Morgan *et al.* (1997) exposed male and female B6C3F$_1$ mice to 0, 25, 50, or 75 ppm divinylbenzene-55 in air 6 hours per day, 5 days per week for up to 2 weeks. Six mice per sex per group were killed after three, five, and 10 exposures, and six mice per sex in the 75 ppm group were killed 7 days after the tenth exposure. The most severe effects occurred in the nasal cavity and liver with less severe effects in the kidneys. In the nasal cavity olfactory epithelium, acute necrosis and inflammation were present at early time points followed by regeneration, architectural reorganization, and focal respiratory metaplasia by 7 days after the last exposure. Olfactory epithelial changes were concentration-dependent with extensive involvement at 75 ppm and peripheral sparing at 25 ppm. There were also necrosis and regeneration of olfactory-associated Bowman's glands as well as the lateral nasal (Steno's) glands. Hepatocellular centrilobular necrosis was observed only in the 75 ppm group and was similar to that caused by styrene. A time-dependent progression was observed, characterized by centrilobular degeneration after one exposure, necrosis after three and five exposures, and chronic inflammation with centrilobular karyomegaly after 10 exposures and 7 days after the tenth exposure. Hepatic concentrations of reduced glutathione were decreased in a dose-dependent manner throughout the 2-week study. In the kidneys, transient tubular damage observed in some male mice exposed to 75 ppm appeared to be a response to divinylbenzene-induced tubular epithelial injury.

Humans

There was no data available on the toxicity of divinylbenzene in humans.

Reproductive and Developmental Toxicity

There was no data available on the reproductive and developmental toxicity of divinylbenzene in experimental animals or humans.

Carcinogenicity

There have been no carcinogenicity studies of divinylbenzene in experimental animals or epidemiology studies in humans.

Genetic Toxicity

Zeiger *et al.* (1987) reported that divinylbenzene-55 was negative for mutagenicity in *Salmonella* strains TA98, TA100, TA1535, and TA1537 at concentrations up to 666 µg/plate both with and without microsomal activation. In an abstract (Knaap *et al.*, 1985), a Dutch research group examined a 70% mixture of divinylbenzene isomers in ethylvinylbenzene in a fluctuation test with *Klebsiella pneumoniae* to a concentration of 55 µL/L, the Ames assay with TA98 and TA100 with and without activation up to 0.5 µL/plate, the sex-linked recessive lethal test in *Drosophila* at 100 µmol/L by injection, and the L5178Y mouse lymphoma mutation system (TK^{-} and HPR^{-} mutation assays) with and without activation from 6×10^{-3} to 18×10^{-3} µL/mL. Divinylbenzene (70%) was uniformly negative in all tests.

Kligerman *et al.* (1996) investigated the genotoxic potential of divinylbenzene-55 in $B6C3F_1$ mice following a 3-day inhalation exposure (6 hours per day) to 0, 25, 50, or 75 ppm. Following exposure, blood smears were prepared for micronucleus analysis, and the spleens were removed and cultured for sister chromatid exchange and chromosomal aberration analyses. Divinylbenzene-55 induced a dose-dependent increase in sister chromatid exchange with the two highest concentrations reaching statistical significance. Similarly, there were statistically significant, although less pronounced, increases in the frequencies of chromosomal aberrations in splenocytes and micronuclei in polychromatic erythrocytes. There was no indication of toxicity as measured by cell cycle kinetics in the splenocytes or the percentage of polychromatic erythrocytes in the peripheral blood smears. The authors concluded that divinylbenzene-55 was a weak genotoxicant.

Study Rationale

The toxicity and carcinogenicity of inhaled divinylbenzene was investigated because of the potential for worker exposure and the structural similarity of divinylbenzene to styrene, a potential human carcinogen (IARC, 1987). The bifunctionality conferred by the two vinyl groups makes divinylbenzene a highly reactive cross-linking agent that may also contribute to its toxicity.

MATERIALS AND METHODS

Procurement and Characterization of Divinylbenzene-HP

Divinylbenzene-HP (80% divinylbenzene with 20% ethylvinylbenzene) was obtained from Dow Chemical Company (Midland, MI) in two lots (LJ31012V18 and ND13012V23). Lot LJ31012V18 was used in the 2-week and 3-month studies, and lot ND13012V23 was used during the 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC); Chemir/Polytech Laboratories, Inc. (Maryland Heights, MO); and the study laboratory, Battelle Northwest Operations (Richland, WA). Reports on analyses performed in support of the divinylbenzene-HP studies are on file at the National Institute of Environmental Health Sciences.

Lots LJ31012V18 and ND13012V23, pale, straw-colored liquids with a hydrocarbon odor, were identified as divinylbenzene-HP using infrared (IR) and proton nuclear magnetic resonance (NMR) spectroscopy and gas chromatography/mass spectrometry (GC/MS). The IR, proton NMR, and GC/MS spectra were consistent with reference and literature spectra of divinylbenzene-HP.

The purity of both lots was determined using GC with flame ionization detection (FID). For both lots, elemental analyses and moisture analyses by Karl Fischer titration were performed, and concentrations of 4-*tert*-butylcatechol added as a polymerization inhibitor were measured using GC, high-performance liquid chromatography (HPLC), or ultraviolet/visible (UV/Vis) spectroscopy. Polymer concentrations were measured in both lots using a UV/Vis turbidity assay.

For lot LJ31012V18, elemental analyses for carbon and hydrogen were in agreement with the theoretical values for divinylbenzene-HP (80% divinylbenzene with 20% ethylvinylbenzene). Karl Fischer titration indicated a moisture content of 87 ± 5 ppm. Polymer content and 4-*tert*-butylcatechol concentrations were well within the specifications of < 20 ppm and > 600 ppm, respectively. GC/FID and GC/MS detected four major peaks that were identified as the *meta*- and *para*-isomers of divinylbenzene and ethylvinylbenzene; the percent total area of the divinylbenzene isomers was 79.3%. GC/FID and GC/MS, using different systems, detected four major peaks and two minor impurity peaks; the minor peaks had areas of approximately 0.1% of the total peak area. The percent total area of the divinylbenzene isomers was 80.2%. Measured as the sum of the *meta*- and *para*-isomers of divinylbenzene, the overall purity of lot LJ31012V18 was determined to be approximately 80%.

For lot ND13012V23, elemental analyses for carbon, hydrogen, nitrogen, and sulfur were in agreement with the theoretical values for divinylbenzene-HP. Karl Fischer titration indicated a moisture content of approximately 200 ppm. Polymer content and 4-*tert*-butylcatechol concentrations were well within the specifications of < 20 ppm and > 600 ppm, respectively. GC/FID and GC/MS, using different systems, detected four major peaks that were identified as the *meta*- and *para*-isomers of divinylbenzene and ethylvinylbenzene; the percent total area of the divinylbenzene isomers was 81.2%. GC/FID indicated a purity exceeding 99.9% relative to a reference standard. GC/FID and GC/MS, using different systems, detected four major peaks and one minor impurity peak having an area percent of 0.13%; the retention time of this minor peak matched that of naphthalene. The percent total area of the divinylbenzene isomers was 81%. Measured as the sum of the *meta*- and *para*-isomers of divinylbenzene, the overall purity of lot ND13012V23 was determined to be approximately 81%. The bulk chemical was stored in its original shipping containers, 5-gallon metal pails, at approximately –20° C. Periodic reanalyses of area percent purity and purity relative to a reference standard stored at –70° C were conducted during the 3-month and 2-year studies with GC/FID. Periodic reanalyses of polymer and 4-*tert*-butylcatechol content were conducted using GC/FID and HPLC during the 3-month and 2-year studies, respectively. No degradation of the bulk chemical was detected, and polymer and 4-*tert*-butylcatechol concentrations remained within the specifications of < 20 ppm and > 600 ppm, respectively.

Vapor Generation and Exposure System

Preheated divinylbenzene-HP was pumped onto glass beads in a heated glass column where it was vaporized. Heated air flowed through the column and carried the vapor out of the generator. Generator output was controlled by the delivery rate of the chemical metering pump.

The vapor was transported to the exposure room at an elevated temperature to prevent condensation. In the exposure room, the vapor was mixed with additional heated air before entering a short vapor distribution manifold. Concentration in the manifold was determined by the chemical pump rate, generator air flow rate, and dilution air flow rate.

An electronically actuated metering valve controlled the flow to each chamber; a pneumatically operated chamber exposure shutoff valve in line with the metering valve stopped flow to the chamber. In addition, for the chambers used for the two lowest exposure concentrations in each study, a compressed air vacuum pump was attached to the chamber end of the delivery line and used for fine control of the vapor delivery rate. When the exposure started, the chamber exposure valves were opened to allow the vapor to flow through the metering valves and then through temperature-controlled delivery lines to each exposure chamber. The vapor was then injected into the chamber inlet duct where it was further diluted with conditioned chamber air to achieve the desired exposure concentration.

The study laboratory designed the inhalation exposure chamber (H-2000; Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chamber with the catch pans in place. The total active mixing volume of each chamber was 1.7 m^3. A condensation particle counter (Model 3022A, TSI, Inc., St. Paul, MN) was used to count the particles in the rooms (2-week and 3-month studies) and all exposure chambers (all studies) before the start of generation and during generation to determine whether divinylbenzene-HP vapor, and not aerosol, was produced. Low levels of particulate material above that typically observed as background in control and treated chambers were detected in exposure chambers during the 3-month studies. However, there was no consistent difference between measurements made before and during exposure and no trend toward increased particulate levels with increased concentration except for the 400 ppm chamber in the 13-week study, which showed slightly higher particulate levels compared to other chambers. In the 3-month studies, there was no airflow in the heated delivery lines between exposures. During the 2-year studies, a continuous flow of compressed air through the heated delivery lines was continued between exposures as well as during the exposures to purge the system of any divinylbenzene that might subsequently form aerosols or polymerize. Measurements before and during 2-year study exposure periods did not show any significant particulate levels above background, even in the 400 ppm chambers.

Vapor Concentration Monitoring

Concentrations of divinylbenzene-HP in the exposure chambers were monitored by an on-line gas chromatograph equipped with FID. Samples were drawn from each exposure chamber approximately every 36 minutes using Hastelloy-C gas-sampling and stream-select valves in a separate, heated valve oven.

The on-line gas chromatograph was checked throughout the day for instrument drift by analyzing an on-line standard of 1,4-diethylbenzene in nitrogen supplied by a diffusion tube standard generator. The on-line gas chromatograph was calibrated during routine exposure periods by a comparison of chamber concentration data to data from grab samples that were collected with charcoal sampling tubes, extracted with toluene containing 1-phenylhexane as an internal standard, and analyzed by an off-line gas chromatograph. The volumes of gas were sampled at a constant flow rate ensured by a calibrated critical orifice. The off-line gas chromatograph was calibrated with gravimetrically prepared standards of divinylbenzene-HP and the internal standard (1-phenylhexane) in toluene.

Chamber Atmosphere Characterization

Buildup and decay rates for chamber vapor concentrations were determined with animals present in the chambers. At a chamber airflow rate of 15 air changes per hour, the theoretical value for the time to achieve 90% of the target concentration after the beginning of vapor generation (T_{90}) and the time for the chamber concentration to decay to

10% of the target concentration after vapor generation was terminated (T_{10}) was approximately 12.5 minutes. Based on experimental data, a T_{90} value of 12 minutes was selected for all studies.

Throughout the studies, concentration uniformity, persistance and stability of the chemical, and degradation impurities were monitored in the chambers. Chamber concentration uniformity was maintained, no degradation was observed, and no impurities other than those in the bulk chemical were observed.

2-Week Studies

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic (Germantown, NY). On receipt, the rats and mice were 4 weeks old. Animals were quarantined for 13 days and were 6 weeks old on the first day of the studies. Groups of five male and five female rats and mice were exposed by whole body inhalation to divinylbenzene-HP at target concentrations of 0, 25, 50, 100, 200, or 400 ppm 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 12 exposures over a period of 16 days (rats) or 13 exposures over a period of 17 days (mice). Feed was available *ad libitum* except during exposure periods; water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded daily for rats and mice. The animals were weighed initially, on days 4 and 13, and at the end of the studies. At the end of the studies, serologic analyses were performed on chamber control rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix K). Details of the study design and animal maintenance are summarized in Table 2.

Necropsies were performed on all rats and mice. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Histopathologic examinations of the kidney, liver, lung, and nose were performed on rats and mice from the chamber control and 400 ppm groups, and the remaining groups were examined to a no-effect level. Table 2 lists the tissues and organs examined.

3-Month Studies

The 3-month studies were conducted to evaluate the cumulative toxic effects of repeated exposure to divinylbenzene-HP and to determine the appropriate exposure concentrations to be used in the 2-year studies. Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic (Germantown, NY). On receipt, the rats and mice were 4 weeks old. Animals were quarantined for 13 to 14 days and were 6 weeks old on the first day of the studies. Before the studies began, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female clinical pathology rats and five male and five female chamber control mice using the protocols of the NTP Sentinel Animal Program (Appendix K).

Groups of 10 male and 10 female rats were exposed to divinylbenzene-HP at concentrations of 0, 25, 50, 100, 200, or 400 ppm for 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 14 weeks; additional groups of 10 male and 10 female clinical pathology study rats were exposed to the same concentrations for 23 days. Groups of 10 male and 10 female mice were exposed to divinylbenzene-HP at concentrations of 0, 12.5, 25, 50, 100, or 200 ppm for 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 14 weeks. Feed was available *ad libitum* except during exposure periods; water was available *ad libitum*. All animals were housed individually. Clinical findings were recorded twice daily for rats and mice. Core study animals were weighed initially, on day 10 or 11, weekly thereafter, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 2.

Animals were anesthetized with carbon dioxide, and blood was collected from the retroorbital sinus of clinical pathology rats on days 3 and 23 and from core study rats at study termination for hematology and clinical chemistry analyses. Blood was collected from the supraorbital sinus of mice at the end of the study for hematology analyses. Samples for hematology analyses were placed in microcollection tubes containing potassium EDTA; samples for clinical chemistry evaluations were placed in similar tubes containing a separator gel. Packed cell volume; hemoglobin concentration; erythrocyte, platelet, and leukocyte counts; mean cell volume; mean cell hemoglobin; and mean cell hemoglobin concentration were determined with a Roche Cobas Helios hematology analyzer (Roche Diagnostics, Branchburg, NJ). Manual hematocrit values were determined using a Damon/IEC MB microcentrifuge (International Equipment Company, Needham Heights, MA) and capillary reader (Damon IEC) for comparison to Cobas values for packed cell volume. A Miller disc was used to determine reticulocyte counts from smears prepared with blood stained with new methylene blue. Blood smears were prepared and stained using a Wescor Aerospray 7100 slide stainer (Wescor, Inc., Logan, UT). Classifying the leukocytes in a minimum 100-cell count completed the leukocyte differential. For clinical chemistry analyses, serum samples were analyzed using Roche Cobas Fara methodologies. The parameters measured are listed in Table 2.

At the end of the 3-month studies, samples were collected for sperm count and motility and vaginal cytology evaluations on rats exposed to 0, 100, 200, or 400 ppm and mice exposed to 0, 25, 50, or 100 ppm. The parameters evaluated are listed in Table 2. For 12 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left testis and left epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

Necropsies were performed on all core study animals. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin. Complete histopathologic examinations were performed on chamber control rats and those exposed to 400 ppm divinylbenzene-HP; the lung and nose were examined in all groups, and the remaining tissues were examined to a no-effect level in the remaining groups. Complete histopathologic examinations were performed on 0, 100, and 200 ppm mice, and the tissues in the remaining groups were examined to a no effect level. Table 2 lists the tissues and organs routinely examined.

2-Year Studies

Study Design

Groups of 50 male and 50 female rats were exposed to divinylbenzene-HP at concentrations of 0, 100, 200, or 400 ppm 6 hours plus T_{90} (12 minutes) per day, 5 days per week for up to 105 weeks. Groups of 50 male and 50 female mice were exposed to divinylbenzene-HP at concentrations of 0, 10, 30, or 100 ppm, 6 hours plus T_{90} (12 minutes) per day, 5 days per week for up to 105 weeks.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic (Germantown, NY) for use in the 2-year studies. Rats and mice were quarantined for 11 days before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 4 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

Animal Maintenance

All rats and mice were housed individually. Feed was available *ad libitum* except during exposure periods; water was available *ad libitum*. Cages and racks were changed and rotated once weekly. Further details of animal maintenance are given in Table 2. Information on feed composition and contaminants is provided in Appendix J.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings and body weights (after initial weights on day 1) were recorded on week 5, every 4 weeks through week 89, at week 92, then every 2 weeks, and at terminal sacrifice.

Complete necropsies and microscopic examinations were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all collected tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. For extended evaluation of renal proliferative lesions, kidneys were step sectioned at 1 mm intervals from the residual cross sectional half of the right kidney and the longitudinal half of the left kidney from male rats. Sectioning of the left and right kidney resulted in a maximum of four sections per kidney. Tissues examined microscopically are listed in Table 2.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the brain, liver, lung, nose, pituitary gland, pleura, and spleen of male and female rats; the kidney and pancreas of male rats; the adrenal cortex, eye, liver, lung, and nose of male and female mice; and the kidney of male mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al.* (1986).

TABLE 2
Experimental Design and Materials and Methods in the Inhalation Studies of Divinylbenzene-HP

2-Week Studies	3-Month Studies	2-Year Studies
Study Laboratory		
Battelle Northwest Operations (Richland, WA)	Battelle Toxicology Northwest (Richland, WA)	Battelle Toxicology Northwest (Richland, WA)
Strain and Species		
F344/N rats B6C3F$_1$ mice	F344/N rats B6C3F$_1$ mice	F344/N rats B6C3F$_1$ mice
Animal Source		
Taconic (Germantown, NY)	Taconic (Germantown, NY)	Taconic (Germantown, NY)
Time Held Before Studies		
13 days	Male rats and mice: 13 days Female rats and mice: 14 days	11 days
Average Age When Studies Began		
6 weeks	6 weeks	6 weeks
Date of First Exposure		
February 23, 1998	Male rats and mice: June 22, 1998 Female rats and mice: June 23, 1998	Rats: September 13, 1999 Mice: September 27, 1999
Duration of Exposure		
Rats: 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 16 days (12 exposures) Mice: 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 17 days (13 exposures)	6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 14 weeks	6 hours plus T_{90} (12 minutes) per day, 5 days per week, for up to 105 weeks
Date of Last Exposure		
Rats: March 10, 1998 Mice: March 11, 1998	Rats: September 21, 1998 (males); September 22, 1998 (females) Mice: September 23, 1998 (males); September 24, 1998 (females)	Rats: September 13, 2001 Mice: September 27, 2001
Necropsy Dates		
Rats: March 11, 1998 Mice: March 12, 1998	Rats: September 22, 1998 (males); September 23, 1998 (females) Mice: September 24, 1998 (males); September 25, 1998 (females)	Rats: September 10-14, 2001 Mice: September 24-28, 2001
Average Age at Necropsy		
8 weeks	19 weeks	110 weeks
Size of Study Groups		
Five males and five females	Core studies: 10 males and 10 females Clinical pathology study: 10 male and 10 female rats Mice: 10 males and 10 females	50 males and 50 females

TABLE 2
Experimental Design and Materials and Methods in the Inhalation Studies of Divinylbenzene-HP

2-Week Studies	3-Month Studies	2-Year Studies
Method of Distribution		
Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 2-week studies	Same as 2-week studies
Animals per Cage		
1	1	1
Method of Animal Identification		
Tail tattoo	Tail tattoo	Tail tattoo
Diet		
NTP-2000 irradiated pellets (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, except during exposure periods, changed weekly	Same as 2-week studies	Same as 2-week studies
Water		
Tap water (Richland, WA, municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as 2-week studies	Same as 2-week studies
Cages		
Stainless-steel wire-bottom (Hazleton System, Inc., Aberdeen, MD), changed weekly	Same as 2-week studies	Stainless-steel wire-bottom (Lab Products, Inc., Seaford, DE), changed weekly
Chamber Air Supply Filters		
Single HEPA (Northland Filter System International; Mechanicville, NY), charcoal (RSE, Inc.; New Baltimore, MI), Purafil (Environmental Systems, Lynnwood, WA)	Same as 2-week studies	Single HEPA (Environmental Filter; Santa Rosa, CA), charcoal (RSE, Inc; New Baltimore, MI), Purafil (Environmental Systems; Lynnwood, WA), changed weekly with chambers, rotated weekly in chambers
Chambers		
Stainless-steel with excreta pan suspended below each cage unit (Harford System, Division of Lab Products, Inc.; Aberdeen, MD)	Same as 2-week studies	Stainless-steel chambers, excreta pan at each of six levels (Lab Products, Inc., Seaford, DE), excreta pans changed daily
Chamber Environment		
Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Chamber air changes: 10/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Chamber air changes: 10/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Chamber air changes: 10/hour
Exposure Concentrations		
0, 25, 50, 100, 200, or 400 ppm in air	Rats: 0, 25, 50, 100, 200, or 400 ppm in air Mice: 0, 12.5, 25, 50, 100, or 200 ppm in air	Rats: 0, 100, 200, or 400 ppm in air Mice: 0, 10, 30, or 100 ppm in air

Table 2
Experimental Design and Materials and Methods in the Inhalation Studies of Divinylbenzene-HP

2-Week Studies	3-Month Studies	2-Year Studies
Type and Frequency of Observation		
Observed twice daily; clinical findings recorded daily postexposure; body weights recorded on days 1, 6, 13, and at terminal sacrifice.	Observed twice daily; body weights recorded day 1, weights and clinical findings recorded days 10 (females) or 11 (males), weekly thereafter, and at terminal sacrifice on core study rats and mice	Observed twice daily; body weights recorded day 1, clinical findings and body weights recorded week 5 and every 4 weeks thereafter through week 89, week 92 and every 2 weeks thereafter, and at terminal sacrifice
Method of Sacrifice		
Carbon dioxide asphyxiation	Same as 2-week studies	Same as 2-week studies
Necropsy		
Necropsies were performed on all animals. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.	Necropsies were performed on all core study animals. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.	Necropsies were performed on all animals.
Clinical Pathology		
None	Blood was collected from the retroorbital sinus of clinical pathology study rats on days 3 and 23 and from core study rats at the end of the study for hematology and clinical chemistry; blood was collected from the supraorbital sinus of mice at the end of the study for hematology. ***Hematology:*** automated and manual hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte and platelet morphology; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials ***Clinical chemistry:*** urea nitrogen, creatinine, total protein, albumin, globulin, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, and total bile acids	None

Table 2
Experimental Design and Materials and Methods in the Inhalation Studies of Divinylbenzene-HP

2-Week Studies	3-Month Studies	2-Year Studies
Histopathology		
Histopathology was performed on 0 and 400 ppm animals. In addition to gross lesions and tissue masses, the following tissues were examined: kidney, liver, lung, and nose. These tissues were examined to a no-effect level in the remaining groups.	Complete histopathology was performed on 0 and 400 ppm rats and 0, 100, and 200 ppm mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone, brain, clitoral gland, esophagus, eye, gallbladder (mice only), heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung and mainstem bronchi, lymph nodes (bronchial, mandibular, mediastinal, mesenteric), mammary gland, thigh muscle, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicles, thymus, thyroid gland, trachea, urinary bladder, and uterus. The lung and nose were examined in all remaining groups of rats, and other tissues in rats and mice were examined to a no-effect level.	Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone, brain, clitoral gland, esophagus, eye, gallbladder (mice only), harderian gland, heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung and mainstem bronchi, lymph nodes (bronchial, mandibular, mediastinal, mesenteric), mammary gland, thigh muscle, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicles, thymus, thyroid gland, trachea, urinary bladder, and uterus
Sperm Motility and Vaginal Cytology		
None	At the end of the studies, sperm samples were collected from male rats in the 0, 100, 200, and 400 ppm groups and from male mice in the 0, 25, 50, and 100 ppm groups for sperm motility evaluations. The following parameters were evaluated: spermatid heads per testis and per gram testis, spermatid counts, and epididymal spermatozoal motility and concentration. The left cauda, left epididymis, and left testis were weighed. Vaginal samples were collected for up to 12 days during the last 2 weeks of the study from female rats in the 0, 100, 200, and 400 ppm groups and from female mice in the 0, 25, 50, and 100 ppm groups for vaginal cytology evaluations. The percentage of time spent in the various estrous cycle stages and estrous cycle length were evaluated.	None

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes or missing were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible concentration-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, only to site-specific, lesion-free animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F$_1$ mice (Portier *et al.,* 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions is represented as 1–P with the letter N added (e.g., P=0.99 is presented as P=0.01N).

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which historically have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, spermatid, and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley

(1977) (as modified by Williams, 1986) and Dunn (1964). Jonckheere's test (1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1957) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure concentrations.

Historical Control Data

The concurrent control group represents the most valid comparison to the treated groups and is the only control group analyzed statistically in NTP bioassays. However, historical control data are often helpful in interpreting potential treatment-related effects, particularly for uncommon or rare neoplasm types. For meaningful comparisons, the conditions for studies in the historical database must be generally similar. One significant factor affecting the background incidence of neoplasms at a variety of sites is diet. In 1995, the NTP incorporated a new diet (NTP-2000) that contains less protein and more fiber and fat than the NIH-07 diet previously used in toxicity and carcinogenicity studies (Rao, 1996, 1997). The current NTP historical database contains all studies that use the NTP-2000 diet with histopathology findings completed up to the present. A second potential source of variability is route of administration. In general, the historical database for a given study will include studies using the same route of administration, and the overall incidences of neoplasms for all routes of administration are included for comparison, including the present study.

Quality Assurance Methods

The 3-month and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of divinylbenzene was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and increases in the frequency of micronucleated erythrocytes in mouse peripheral blood. The protocols for these studies and the results are given in Appendix E. The genetic toxicity studies have evolved from an earlier effort by the NTP to develop a comprehensive database permitting a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). The short-term tests were originally developed to clarify proposed mechanisms of chemical-induced DNA damage based on the relationship between electrophilicity and mutagenicity (Miller and Miller, 1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). However, it should be noted that not all cancers arise through genotoxic mechanisms. DNA reactivity combined with *Salmonella* mutagenicity is highly correlated with induction of carcinogenicity in multiple species/sexes of rodents and at multiple tissue sites (Ashby and Tennant, 1991). A positive response in the *Salmonella* test was shown to be the most predictive *in vitro* indicator for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) (Tennant *et al.,* 1987; Zeiger *et al.,* 1990). Additionally, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. However, these other tests can provide useful information on the types of DNA and chromosomal damage induced by the chemical under investigation.

The predictivity for carcinogenicity of a positive response in acute *in vivo* bone marrow chromosome aberration or micronucleus tests appears to be less than that in the *Salmonella* test (Shelby *et al.,* 1993; Shelby and Witt, 1995). However, clearly positive results in long-term peripheral blood micronucleus tests have high predictivity for rodent carcinogenicity (Witt *et al.,* 2000); negative results in this assay do not correlate well with either negative or positive results in rodent carcinogenicity studies. Because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical. Most organic chemicals that are identified by the International Agency for Research on Cancer as human carcinogens, other than hormones, are genotoxic. The vast majority of these are detected by both the *Salmonella* assay and rodent bone marrow cytogenetics tests (Shelby, 1988; Shelby and Zeiger, 1990).

RESULTS

RATS

2-WEEK STUDY

All rats survived to the end of the study (Table 3). Final mean body weights and body weight gains of 400 ppm rats were significantly less than those of the chamber controls, as were body weight gains of 100 ppm males and 200 ppm males and females. A clear serous nasal/eye discharge was observed in groups of rats exposed to 100 ppm or greater. Lethargy was observed in 400 ppm males on the first day of exposure.

TABLE 3
Survival and Body Weights of Rats in the 2-Week Inhalation Study of Divinylbenzene-HP

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	5/5	86 ± 3	151 ± 5	65 ± 4	
25	5/5	84 ± 5	152 ± 6	68 ± 2	100
50	5/5	86 ± 5	155 ± 6	69 ± 3	103
100	5/5	83 ± 3	138 ± 2	55 ± 3*	91
200	5/5	83 ± 3	142 ± 5	58 ± 2*	94
400	5/5	84 ± 4	135 ± 5*	52 ± 2**	90
Female					
0	5/5	70 ± 2	112 ± 2	42 ± 1	
25	5/5	71 ± 2	115 ± 2	44 ± 2	103
50	5/5	69 ± 2	112 ± 3	43 ± 2	100
100	5/5	71 ± 2	111 ± 2	40 ± 1	99
200	5/5	70 ± 2	106 ± 2	36 ± 1*	95
400	5/5	70 ± 2	104 ± 2*	34 ± 1**	92

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' test
** $P \leq 0.01$
a Number of animals surviving at 2 weeks/number initially in group
b Weights and weight changes are given as mean ± standard error.

Relative kidney weights of 50 ppm or greater males and relative liver weights of 200 and 400 ppm males were significantly greater than those of the chamber controls (Table G1). In addition, liver, kidney, and lung weights of exposed groups of female rats were generally greater than those of the chamber controls.

The only histologic change observed was minimal or mild rhinitis in 400 ppm rats of both sexes. Rhinitis was present in Section 1, the most cranial section of the nose, taken just caudal to the caudal aspect of the upper incisor teeth. Inflammatory cell infiltrates, composed of lymphocytes and polymorphonuclear leukocytes, were largely within the epithelium and subjacent connective tissue. To a lesser extent, polymorphonuclear leukocytes formed small aggregates on the epithelial surface.

Exposure Concentration Selection Rationale: Because there were no effects of divinylbenzene-HP on survival of rats in the 2-week study, and final body weights were within 90% of the control groups, exposure concentrations selected for the 3-month inhalation study in rats were 0, 25, 50, 100, 200, and 400 ppm.

3-Month Study

All rats survived to the end of the study (Table 4). The final mean body weight of 400 ppm males and mean body weight gains of males exposed to 200 or 400 ppm were significantly less than those of the chamber controls. The mean body weight gain of 50 ppm females was significantly greater than that of the chamber controls. Nasal/eye discharge was occasionally noted in groups exposed to 50 ppm or greater.

The hematology and clinical chemistry data for rats in the 3-month study are listed in Table F1. There were changes in the leukon that, in general, would be consistent with a physiological stress/steroid-induced type response in exposed male and female rats. The leukon alterations were, in general, characterized by decreases in leukocyte and lymphocyte counts. These changes were mild (~ 40% or less decrease) and occurred in 400 ppm

Table 4
Survival and Body Weights of Rats in the 3-Month Inhalation Study of Divinylbenzene-HP

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	10/10	77 ± 5	302 ± 4	225 ± 6	
25	10/10	79 ± 4	315 ± 7	236 ± 7	104
50	10/10	79 ± 5	306 ± 4	227 ± 4	101
100	10/10	80 ± 6	300 ± 8	220 ± 5	99
200	10/10	83 ± 4	289 ± 9	207 ± 8*	96
400	10/10	77 ± 5	273 ± 5**	196 ± 6**	90
Female					
0	10/10	84 ± 4	182 ± 3	98 ± 3	
25	10/10	74 ± 4	185 ± 4	110 ± 3	101
50	10/10	81 ± 3	196 ± 4	114 ± 3**	107
100	10/10	79 ± 4	183 ± 3	104 ± 4	101
200	10/10	80 ± 4	177 ± 5	97 ± 3	97
400	10/10	80 ± 3	179 ± 4	98 ± 4	98

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
** $P \leq 0.01$
a Number of animals surviving at 3 months/number initially in group
b Weights and weight changes are given as mean ± standard error.

males and females on days 3 and 23 and in females exposed to 50, 100, or 200 ppm on day 23. These alterations were transient, however, and, by week 14, there were no differences in the leukon between exposed and control animals.

At day 3, there were small (< 10%) increases in erythrocyte counts in 200 and 400 ppm males and 100 ppm or greater females; a small (< 10%) increase in hematocrit values also occurred in 400 ppm males. These were transient findings that generally disappeared by day 23. Blood urea nitrogen concentrations were also transiently increased in males and female rats exposed to 100 ppm or greater; the increases ameliorated with time and were gone by week 14. While there were no changes in albumin or total protein concentrations, it is possible that the transient increase in the erythron and urea nitrogen concentrations was related to dehydration. Other scattered changes in the hematological and clinical chemistry variables occurred but were not considered toxicologically relevant.

Relative kidney and liver weights of all exposed groups of males and of 400 ppm females were greater than those of chamber controls (Table G2). In addition, the relative weights of the heart and testis were significantly increased in 200 and 400 ppm males. There were no corresponding histologic changes to account for the organ weight changes. There were no significant differences between exposed and chamber control groups in reproductive tissue evaluations in males or vaginal cytology parameters in females (Tables H1 and H2).

Although no gross lesions were observed that could be attributed to exposure to divinylbenzene-HP, microscopic lesions were observed in the nose of male and female rats. Incidences of predominately minimal degeneration of the olfactory epithelium were significantly increased in 200 and 400 ppm rats (Table 5). In addition, the incidences of minimal to mild basal cell hyperplasia of the olfactory epithelium were significantly increased in rats exposed to 100 ppm or greater. The severity of these lesions increased with increasing exposure concentration. Olfactory epithelial degeneration was characterized by disorganization and decreased thickness of olfactory epithelium with loss of neuroepithelial cells. Basal cell hyperplasia of olfactory epithelium was characterized by proliferation of basal cells with or without distortion of overlying neuroepithelial cells.

Exposure Concentration Selection Rationale: Because there were no treatment-related effects of divinylbenzene-HP on survival and minimal effects of exposure on body weights, organ weights, and incidences of lesions in the 3-month study, exposure concentrations selected for the 2-year inhalation study in rats were 0, 100, 200, and 400 ppm.

TABLE 5
Incidences of Selected Nasal Lesions in Rats in the 3-Month Inhalation Study of Divinylbenzene-HP

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
Male						
Number Examined Microscopically	10	0	10	10	10	10
Olfactory Epithelium, Degeneration[a]	0		0	1 (1.0)[b]	7** (1.0)	8** (1.1)
Olfactory Epithelium, Basal Cell, Hyperplasia	0		0	9** (1.1)	10** (1.6)	10** (1.9)
Female						
Number Examined Microscopically	10	0	10	10	10	10
Olfactory Epithelium, Degeneration	0		0	2 (1.0)	6** (1.3)	9** (1.3)
Olfactory Epithelium, Basal Cell, Hyperplasia	0		0	5* (1.0)	9** (1.2)	10** (1.8)

* Significantly different ($P \leq 0.05$) from the chamber control group by the Fisher exact test
**$P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

2-Year Study

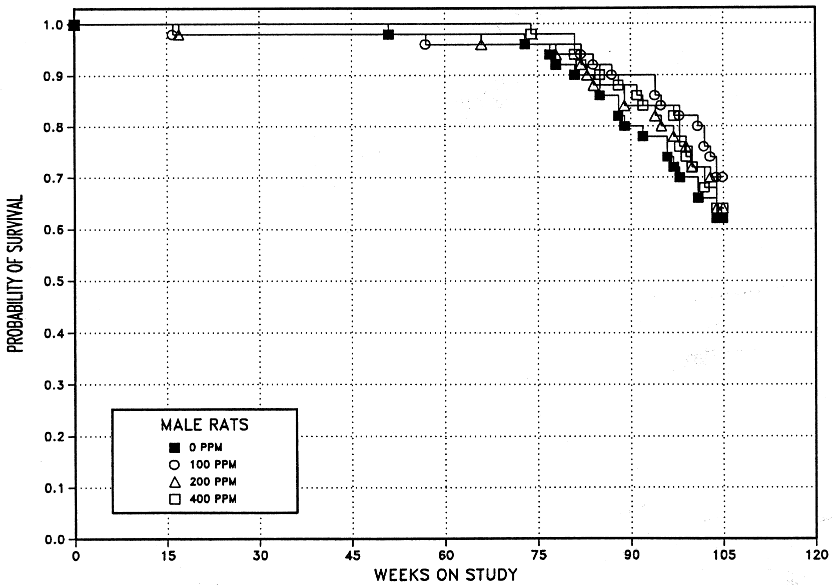
Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 6 and in the Kaplan-Meier survival curves (Figure 3). Survival of 400 ppm females was significantly less than that of the chamber control group. Survival of all exposed groups of males was similar to that of the chamber control group.

Table 6
Survival of Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	15	9	12	13
Natural deaths	4	6	6	5
Animals surviving to study termination	31	35	32[a]	32
Percent probability of survival at end of study[b]	62	70	64	64
Mean survival (days)[c]	686	694	687	700
Survival analysis[d]	P=1.000N	P=0.435N	P=0.907N	P=0.853N
Female				
Animals initially in study	50	50	50	50
Accidental death[e]	0	1	0	0
Moribund	10	16	14	26
Natural deaths	7	3	3	2
Animals surviving to study termination	33	30	33	22
Percent probability of survival at end of study	66	61	66	44
Mean survival (days)	679	690	691	651
Survival analysis	P=0.019	P=0.901	P=1.000N	P=0.049

[a] Includes one animal that died during the last week of the study
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the chamber control column, and the results of the life table pairwise comparisons (Cox, 1972) with the chamber controls are in the exposed group columns. A negative trend or lower mortality in an exposed group is indicated by **N**.
[e] Censored from survival analyses



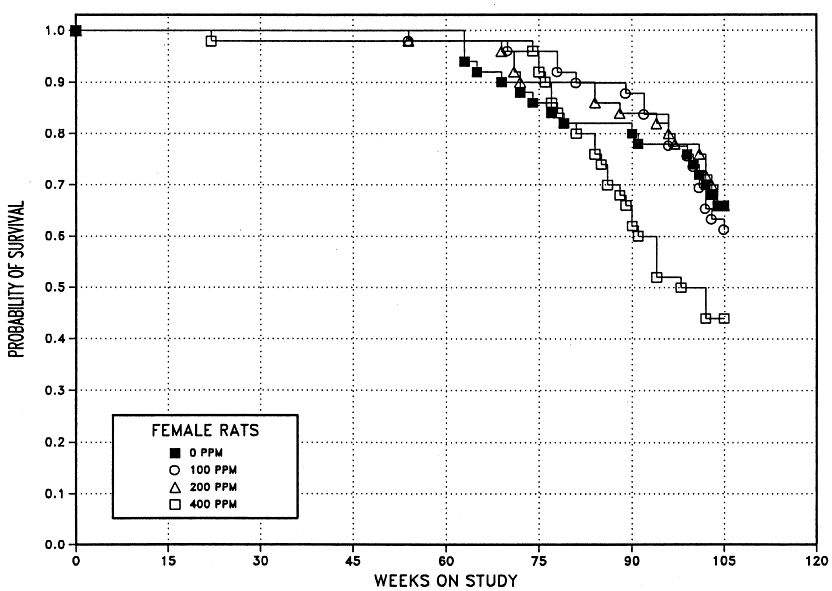


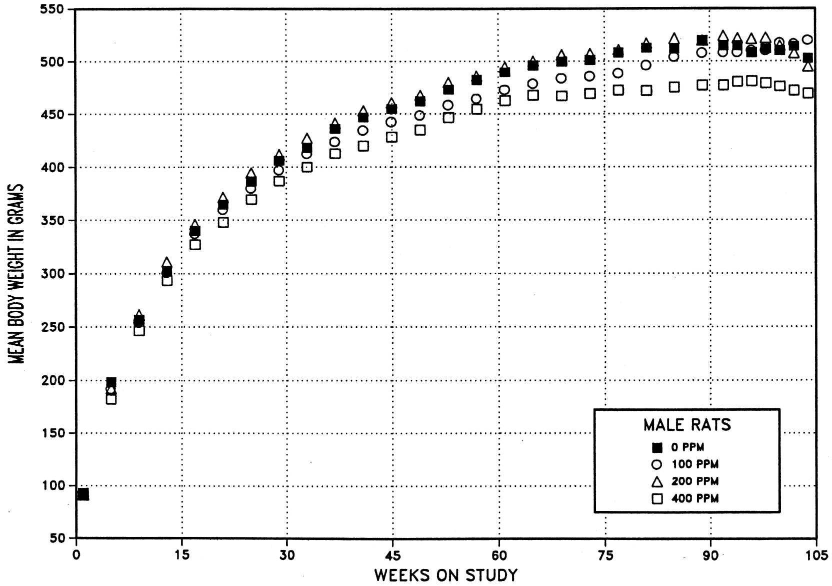
FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Divinylbenzene-HP by Inhalation for 2 Years

Body Weights and Clinical Findings

Mean body weights of 400 ppm males were less than those of the chamber controls from week 37 to the end of the study; mean body weights of 400 ppm females were less than those of the chamber controls during the second year of the study (Figure 4, Tables 7 and 8). An increased incidence of lethargy in 400 ppm males occurred late in the study.

Primarily during the second year of the study, seizures were observed sporadically in a few male and female rats from each exposure group, including chamber controls. More female rats were affected than males (males: 1/50, 4/50, 1/50, 2/50; females: 1/50, 2/50, 6/50, 5/50) and the first onset was earlier in females (week 41) than in males (week 59). Most seizures were mild, characterized by an abnormal hunched posture and chewing movements sometimes accompanied by clonic spasms of alternate muscle contraction and relaxation, and lasted approximately 30 seconds with a rapid recovery. Uncommon seizures of greater severity produced more pronounced jerking motions lasting up to 60 seconds with a recovery time of two minutes. Most seizure-prone animals had multiple episodes (2 to 8), and neither the incidences nor the number of episodes per rat appeared related to exposure concentration.

Similar, sporadic seizures have been observed in F344/N rats in six other NTP inhalation or dermal exposure studies at three different laboratories. In all these studies the single common factor is that the animals were housed individually. No such episodes have been observed in concurrent dosed feed, gavage, or drinking water studies in which rats were group housed. In the individually housed animals, most seizures were observed early in the day, when technical and maintenance activities were commencing following the animals' dark cycle period. No deaths were associated with seizures, and there were no correlations with body weight, feed consumption or composition, or histopathological lesions in this or other studies. Thus these transient events were not considered to have affected the toxicologic or carcinogenicity evaluations of this study.



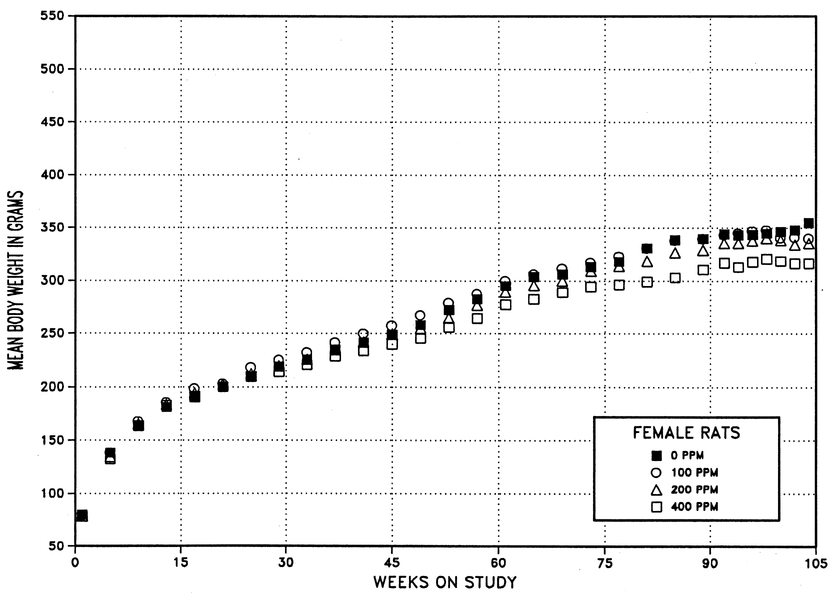


FIGURE 4
Growth Curves for Male and Female Rats
Exposed to Divinylbenzene-HP by Inhalation for 2 Years

Table 7
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

Weeks on Study	Chamber Control Av. Wt. (g)	Chamber Control No. of Survivors	100 ppm Av. Wt. (g)	100 ppm Wt. (% of controls)	100 ppm No. of Survivors	200 ppm Av. Wt. (g)	200 ppm Wt. (% of controls)	200 ppm No. of Survivors	400 ppm Av. Wt. (g)	400 ppm Wt. (% of controls)	400 ppm No. of Survivors
1	93	50	91	98	50	91	98	50	91	98	50
5	198	50	192	97	50	192	97	50	182	92	50
9	257	50	254	99	50	261	102	50	247	96	50
13	303	50	301	99	50	311	103	50	294	97	50
17	340	50	337	99	49	346	102	50	327	96	50
21	365	50	360	99	49	371	102	49	348	95	50
25	387	50	380	98	49	394	102	49	370	96	50
29	406	50	397	98	49	412	101	49	387	95	50
33	418	50	412	99	49	427	102	49	400	96	50
37	436	50	424	97	49	441	101	49	413	95	50
41	447	50	435	97	49	453	101	49	420	94	50
45	455	50	443	97	49	461	101	49	428	94	50
49	462	50	449	97	49	468	101	49	435	94	50
53	473	49	458	97	49	480	101	49	447	94	50
57	482	49	464	96	49	486	101	49	455	94	50
61	490	49	473	97	48	494	101	49	463	95	50
65	496	49	479	97	48	500	101	49	468	94	50
69	500	49	484	97	48	506	101	48	467	94	50
73	501	49	486	97	48	507	101	48	469	94	50
77	508	48	489	96	48	511	101	48	473	93	49
81	513	45	496	97	48	517	101	47	472	92	49
85	512	45	504	99	46	521	102	44	475	93	46
89	520	41	508	98	45	520	100	44	477	92	44
92	515	40	508	99	45	524	102	42	477	93	43
94	515	39	508	99	45	522	101	42	480	93	42
96	508	39	510	100	42	521	103	40	481	95	42
98	512	36	510	100	42	522	102	39	479	94	41
100	510	35	517	101	41	515	101	38	476	93	37
102	514	33	516	100	40	508	99	36	472	92	36
104	503	33	520	103	37	495	98	35	469	93	34
Mean for weeks											
1-13	213		210	98		214	100		204	96	
14-52	413		404	98		419	101		392	95	
53-104	504		496	98		509	101		471	93	

Table 8
Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

Weeks	Chamber Control		100 ppm			200 ppm			400 ppm		
on Study	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	80	50	79	98	50	79	98	50	78	98	50
5	139	50	139	100	50	135	97	50	132	96	50
9	164	50	168	102	50	166	101	50	164	100	50
13	181	50	186	102	50	184	101	50	183	101	50
17	190	50	199	104	50	194	102	50	191	101	50
21	200	50	203	101	50	202	101	50	200	100	50
25	210	50	218	104	50	212	101	50	209	100	49
29	219	50	225	103	50	220	100	50	214	98	49
33	226	50	232	103	50	226	100	50	221	98	49
37	235	50	242	103	50	235	100	50	229	98	49
41	242	50	250	103	50	242	100	50	234	97	49
45	249	50	258	104	50	249	100	50	240	97	49
49	258	50	267	104	50	255	99	50	246	95	49
53	273	50	279	102	50	265	97	50	256	94	49
57	283	50	288	102	49	277	98	49	265	94	49
61	295	50	300	102	49	290	98	49	278	94	49
65	304	47	307	101	49	296	97	49	283	93	49
69	306	46	312	102	49	300	98	49	289	94	49
73	313	44	317	101	48	309	99	45	295	94	49
77	318	43	323	102	47	314	99	45	296	93	45
81	331	41	331	100	45	319	96	45	299	91	41
85	339	41	338	100	44	327	96	43	303	90	38
89	340	41	340	100	44	329	97	42	311	91	34
92	344	39	344	100	43	336	98	42	317	92	30
94	344	39	345	101	41	336	98	42	313	91	30
96	344	39	347	101	41	338	98	41	318	93	26
98	345	39	348	101	38	340	99	39	321	93	26
100	347	38	340	98	37	338	98	39	319	92	25
102	348	36	341	98	34	334	96	38	317	91	25
104	355	33	340	96	31	336	95	35	317	89	22
Mean for weeks											
1-13	141		143	101		141	99		139	99	
14-52	225		233	103		226	100		220	98	
53-104	325		326	100		317	97		300	92	

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of mononuclear cell leukemia and neoplasms and/or nonneoplastic lesions of the kidney, brain, skin, thyroid gland, nose, and lung. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Kidney: In the standard evaluation of the kidney, two 400 ppm males had renal tubule carcinoma; although the higher incidence in this group was marginal and not statistically significant, it exceeded the historical incidence in chamber control male rats (Tables 9, A1, and A4). Marked cortical renal tubule hyperplasia occurred in an additional two 400 ppm males (Tables 9 and A5).

In the kidney, renal tubule hyperplasia, adenoma, and carcinoma are thought to represent a continuum in the progression of proliferative lesions. In the standard evaluation, a single section of each kidney was examined microscopically. Because the marginally greater incidences of renal tubule carcinoma and the greater severity of renal tubule hyperplasia in the 400 ppm males indicated the possibility of a treatment-related carcinogenic effect, an extended evaluation of the kidney was performed in males. In the extended evaluation, renal tubule adenomas were identified in two 200 ppm and one 400 ppm males (Table 9). Additional incidences of renal tubule hyperplasia were also identified in the chamber control and exposed groups. No additional renal tubule carcinomas were identified. In the combined analyses, the incidences of renal tubule adenoma and adenoma or carcinoma (combined) were marginally, but not statistically, higher in 200 and 400 ppm males but exceeded the single section historical incidence for chamber controls (Tables 9, A3, and Aa). Renal tubule hyperplasia was characterized by single or multiple (adjacent) tubules lined by three or more layers of epithelium, partially or completely filling the lumen. There was little cellular atypia, and component cells ranged from smaller than normal to larger than normal epithelial cells. Renal tubule adenomas were well-circumscribed, discrete masses of epithelial cells that caused

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Number Examined Microscopically	50	49	50	49
Single Sections (Standard Evaluation)				
Renal Tubule, Hyperplasia[a]	1 (2.0)[b]	2 (1.0)	0	2 (4.0)
Nephropathy, Chronic	37 (1.8)	41 (1.5)	41 (2.1)	45* (1.8)
Renal Tubule, Carcinoma[c]	0	0	0	2
Step Sections (Extended Evaluation)				
Cortex, Renal Tubule, Hyperplasia	2 (1.0)	3 (1.0)	5 (1.4)	14** (1.7)
Renal Tubule, Adenoma	0	0	2	1
Single and Step Sections (Combined)				
Cortex, Renal Tubule, Hyperplasia	3 (1.3)	5 (1.0)	5 (1.4)	16** (2.0)
Renal Tubule, Adenoma	0	0	2	1
Renal Tubule, Carcinoma	0	0	0	2
Renal Tubule, Adenoma or Carcinoma				
Overall Rate[d]	0/50 (0%)	0/49 (0%)	2/50(4%)	3/49 (6%)
Adjusted Rate[e]	0.0%	0.0%	4.5%	6.8%
Terminal Rate[f]	0/31 (0%)	0/35 (3%)	1/32 (3%)	1/32 (3%)
First Incidence (days)	—[h]	—	619	682
Poly-3 test[g]	P=0.027	—[i]	P=0.244	P=0.123

* Significantly different (P≤0.05) from the chamber control group by the Poly-3 test
** P≤0.01
a Number of animals with lesion
b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
c Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 1/399 (0.3% ± 0.7%), range 0%-2%
d Number of animals with neoplasm per number of animals with kidney examined microscopically
e Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
f Observed incidence at terminal kill
g Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
h Not applicable; no neoplasms in animal group
i Value of statistic cannot be computed

slight compression of surrounding parenchyma. Adenomas were mildly expansile, generally exceeding the diameter of five tubules and were composed of multiple layers or solid sheets of epithelial cells with loss of normal cellular orientation, and occasional microtubular formation. One of the renal tubule carcinomas was composed of mixed tubular and solid arrangements of a heterogeneous population of neoplastic cells with focal cystic areas and hemorrhage. The second carcinoma from the single sections, was solid, composed of sheets and cords of highly anaplastic cells, with evidence of capsular invasion and distant metastases.

The incidences of mild chronic nephropathy were higher in all exposed groups of males and significantly increased in the 400 ppm group (Tables 9 and A5). Chronic nephropathy is an age-associated lesion, particularly common in males, characterized by a spectrum of lesions including glomerulosclerosis, thickening of glomerular and tubular basement membranes proteinaceous tubular casts, tubular dilatation, degeneration and regeneration, interstitial fibrosis, and mononuclear cell infiltration.

Brain: Malignant glial cell tumors occurred in three males in the 200 ppm group (two astrocytomas and one oligodendroglioma) and a single 200 ppm female (astrocytoma). A single male from the 100 ppm group had oligodendroglioma (Tables 10, A1, A3, and B1). The incidence in 200 ppm males exceeded the historical incidence of astrocytoma, glioma, or oligodendroglioma (combined) for chamber controls (Tables 10 and A4b). Although the incidences of these malignant glial cell neoplasms did not increase with increasing exposure concentration, these are rare tumors and association with exposure to divinylbenzene-HP could not be excluded.

Skin: In 400 ppm males, the incidence of basal cell adenoma was marginally higher than chamber controls and exceeded historical control values for basal cell adenoma, basosquamous tumor benign, and trichoepithelioma (combined) (Tables 11, A1, and A3). Tumors were identified grossly as subcutaneous masses on the dorsal, ventral, or lateral aspect of the torso or on the tail. Histologically, basal cell adenomas were well-circumscribed masses composed predominantly of basal cells or a mixture of sebaceous and keratinizing squamous epithelium, often forming cysts. A trichoepithelioma was observed in a control male. Since the basal cell is the common

TABLE 10
Incidences of Neoplasms of the Brain in Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Male				
Number Examined Microscopically	49	50	50	50
Astrocytoma Malignant[a,b]	0	0	2	0
Oligodendroglioma Malignant[c]	0	1	1	0
Oligodendroglioma or Astrocytoma[b]				
Overall Rate[d]	0/49 (0%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rate[e]	0.0%	2.2%	6.8%	0.0%
Terminal Rate[f]	0/30 (0%)	0/35 (0%)	3/32 (9%)	0/32 (0%)
First Incidence (days)	—[h]	582	729 (T)	—
Poly-3 test[g]	P=0.614N	P=0.517	P=0.126	—[i]
Female				
Number Examined Microscopically	50	50	50	50
Astrocytoma Malignant[j]	0	0	1	0

(T) Terminal sacrifice
a Number of animals with neoplasm
b Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 1/398 (0.3% ± 0.7%), range 0%-2%
c Historical incidence: 0/398
d Number of animals with neoplasm per number of animals with brain examined microscopically
e Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
f Observed incidence at terminal kill
g Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend is indicated by **N**.
h Not applicable; no neoplasms in animal group
i Value of statistic cannot be computed
j Historical incidence: 0/397

precursor of both basal cell adenoma and trichoepithelioma, these neoplasms can be combined for statistical analysis. The trichoepithelioma was composed of neoplastic basal cells with prominent hair follicle differentiation. The occurrence of a marginal increase in basal cell adenoma in 400 ppm males only, with no consistent site distribution, was considered unlikely to be related to exposure to divinylbenzene-HP (Table 11).

Table 11
Incidences of Basal Cell Adenoma of the Skin in Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Number of Animals Necropsied	50	50	50	50
Trichoepithelioma[a,b]	1	0	0	0
Basal Cell Adenoma[b]				
Overall Rate[c]	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rate[d]	0.0%	0.0%	2.2%	6.7%
Terminal Rate[e]	0/31 (0%)	0/35 (0%)	0/32 (0%)	3/32 (9%)
First Incidence (days)	—[g]	—	578	729 (T)
Poly-3 test[f]	P=0.020	—[h]	P=0.507	P=0.126
Trichoepithelioma or Basal Cell Adenoma[i]				
Overall Rate	1/50 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rate	2.3%	0.0%	2.2%	6.7%
Terminal Rate	1/31 (3%)	0/35 (0%)	0/32 (0%)	3/32 (9%)
First Incidence (days)	729 (T)	—	578	729 (T)
Poly-3 test	P=0.097	P=0.490N	P=0.753N	P=0.320

T) Terminal sacrifice
a Number of animals with neoplasm
b Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 1/399 (0.3% ± 0.7%), range 0%-2%
c Number of animals with neoplasm per number of animals necropsied
d Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
e Observed incidence at terminal kill
f Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
g Not applicable; no neoplasms in animal group
h Value of statistic cannot be computed
i Historical incidence (includes basosquamous cell tumor benign): 2/399 (0.5% ± 0.9%), range 0%-2%

Mononuclear Cell Leukemia: In females, there was a greater incidence of mononuclear cell leukemia in exposed groups when compared with the concurrent chamber controls. The incidence in all exposed groups was within the historical chamber control range. The concurrent chamber control incidence was below the mean historical control incidence and was at the lower end of the historical control range (Tables 12, B3, and B4). Mononuclear cell leukemia in females was therefore considered to be unrelated to treatment.

In males from all exposed groups, the incidences of mononuclear cell leukemia were decreased and below the historical range for chamber controls (Tables 12 and A3). Decreases were significant at 100 and 400 ppm. Mononuclear cell leukemia is a tumor of large granular lymphocyte origin, which is unique to the rat, and is uncommon in strains other than the F344 rat (Stromberg *et al.*, 1983). In untreated F344 rats it occurs in aged animals at a variable rate in both sexes; although it tends to occur more commonly in males (Haseman *et al.,* 1998). Decreases in the incidence of mononuclear cell leukemia have been seen in both sexes with chemicals causing splenic toxicity (Elwell *et al.,* 1996). In this study decreases occurred only in males, there was no evidence of pathology in the spleen, and the biological significance of this decrease in males is therefore uncertain.

Thyroid Gland: In females, C-cell adenoma occurred in all exposed groups (reaching statistical significance at 100 and 400 ppm), but not in chamber controls (Tables 13 and B3). C-cell carcinoma occurred in single animals in the chamber control, 100, and 200 ppm groups. Incidences of C-cell adenoma and adenoma or carcinoma (combined) were within the historical ranges for chamber controls. The incidence and severity of C-cell hyperplasia also decreased with increasing exposure concentration in females. Incidences of C-cell hyperplasia were generally greater in exposed males and significant at 200 ppm (Tables 13 and A3). However, the incidences of C-cell adenoma and adenoma or carcinoma (combined) were marginally higher in the 100 ppm group only and within the historical chamber control range. In the rat, thyroid gland C-cell hyperplasia, adenoma, and carcinoma represent a continuum of proliferative change. In both sexes, there was a lack of correlation between hyperplastic and

Table 12
Incidences of Mononuclear Cell Leukemia in Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Male				
Mononuclear Cell Leukemia[a]				
Overall Rate[b]	22/50 (44%)	13/50 (26%)	14/50 (28%)	10/50 (20%)
Adjusted Rate[c]	46.4%	27.8%	30.9%	21.5%
Terminal Rate[d]	9/31 (29%)	6/35 (17%)	9/32 (28%)	4/32 (13%)
First Incidence (days)	355	569	544	569
Poly-3 test[e]	P=0.013N	P=0.047N	P=0.092N	P=0.008N
Female				
Mononuclear Cell Leukemia[f]				
Overall Rate	10/50 (20%)	18/50 (36%)	22/50 (44%)	22/50 (44%)
Adjusted Rate	23.0%	38.9%	47.1%	49.7%
Terminal Rate	6/33 (18%)	8/30 (27%)	12/33 (36%)	5/22 (23%)
First Incidence (days)	477	542	481	516
Poly-3 test	P=0.008	P=0.078	P=0.013	P=0.007

[a] Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 188/399 (47.1% ± 10.3%), range 32%- 66%
[b] Number of animals with neoplasm per number of animals necropsied
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[f] Historical incidence: 136/399 (34.1% ± 11.9%), range 20%-52%

neoplastic C-cell lesions. Incidence rates of C-cell adenoma and carcinoma lacked a clear dose response and were within historical control ranges; therefore, thyroid gland C-cell hyperplasia and neoplasia in male and female rats were considered not to be associated with exposure to divinylbenzene-HP.

Table 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Thyroid Gland (C-Cell) in Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Male				
Number Examined Microscopically	50	50	50	49
C-Cell Hyperplasia[a]	2 (2.5)[b]	4 (3.0)	9* (2.6)	7 (2.4)
C-Cell Adenoma[c]	2	5	2	2
C-Cell Carcinoma	1	0	0	1
C-Cell Adenoma or Carcinoma [d]	3	5	2	3
Female				
Number Examined Microscopically	50	50	50	50
C-Cell Hyperplasia	5 (2.8)	8 (2.0)	6 (1.8)	1 (1.0)
C-Cell Adenoma[e]				
Overall Rate[f]	0/50 (0%)	5/50 (10%)	1/50 (2%)	4/50 (8%)
Adjusted Rate[g]	0.0%	11.2%	2.3%	10.4%
Terminal Rate[h]	0/33 (0%)	3/30 (10%)	1/33 (3%)	2/22 (9%)
First Incidence (days)	—[j]	506	731 (T)	563
Poly-3 test[i]	P=0.134	P=0.035	P=0.507	P=0.049
C-Cell Carcinoma	1	1	1	0
C-Cell Adenoma or Carcinoma[k]				
Overall Rate	1/50 (2%)	6/50 (12%)	2/50 (4%)	4/50 (8%)
Adjusted Rate	2.4%	13.4%	4.6%	10.4%
Terminal Rate	0/33 (0%)	3/30 (10%)	1/33 (3%)	2/22 (9%)
First Incidence (days)	716	506	715	563
Poly-3 test	P=0.282	P=0.064	P=0.512	P=0.150

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test
(T) Terminal sacrifice
a Number of animals with lesion
b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
c Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 35/395 (9.0% ± 6.5%), range 2%-20%
d Historical incidence: 43/395 (11.0% ± 6.7%), range 2%-22%
e Historical incidence: 31/392 (8.0% ± 5.1%), range 0%-16%
f Number of animals with neoplasm per number of animals with thyroid gland examined microscopically
g Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
h Observed incidence at terminal kill
i Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
j Not applicable; no neoplasms in animal group
k Historical incidence: 44/392 (11.3% ± 6.0%), range 2%-18%

Nose: Adenoma of the respiratory epithelium occurred in one 400 ppm female (Tables 14 and B1). This lesion has not been observed in historical chamber control female rats (0/397), but occurs in a single female 1/1,454 (range 0% to 1%) in the wider historical control database (all routes of administration). In addition, whereas the nose was a target organ in this study, in other studies with similar nonneoplastic lesions, nasal adenomas were not observed. Review of published NTP technical reports between 1990 and 2004 showed that of 17 chronic inhalation studies in F344/N rats in which there were nonneoplastic nasal changes, 15 had no nasal adenomas. In the two studies in which nasal adenomas were seen, the chemicals were clear nasal carcinogens or occurred in multiple animals and were not the only nasal tumor seen (furfuryl alcohol; NTP, 1999; naphthalene: NTP, 2000). The occurrence of a single nasal tumor in the high dose group of one sex was, therefore, insufficient to be considered evidence of a neoplastic response to divinylbenzene-HP exposure. There was an increased incidence of minimal to mild degeneration and basal cell hyperplasia of the olfactory epithelium in all exposed groups of rats, and the incidences increased with increasing exposure concentration (Tables 14, A5, and B5). The incidences of Bowman's gland dilatation were increased in all exposed groups of rats. The incidences of respiratory epithelial goblet cell hyperplasia in male rats were increased in the 200 and 400 ppm groups, and higher in the 100 ppm group. The mean severity of this lesion, however, did not increase with exposure concentration. Slightly higher incidences of minimal to mild suppurative inflammation occurred in the nasal epithelium and lamina propria of both sexes and was statistically significant in 200 ppm males.

Microscopically, olfactory epithelial degeneration consisted of a combination of focal to multifocal disorganization and atrophy, characterized by loss of sensory cells with a decrease in the number of layers of olfactory neuroepithelium. There were occasional small accumulations of necrotic debris, usually involving the medial septum and dorsal meatus of level III, and to a lesser extent level II. Olfactory epithelial basal cell hyperplasia was characterized by focal to extensive proliferation of basal cells and graded mild to moderate depending on the extent of replacement of normal epithelial architecture and depth of extension into the lamina propria by basal cells (Plates 1 and 2). Dilatation of Bowman's glands (up to three times the normal diameter) was most apparent in the medial septum of level II. Glands contained small amounts of eosinophilic material and were lined by flattened,

TABLE 14
Incidences of Selected Neoplasms and Nonneoplastic Lesions of the Nose and Lung in Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Male				
Nose[a]	50	48	50	49
Olfactory Epithelium, Degeneration[b]	0	47** (1.6)[c]	49** (1.7)	49** (2.0)
Olfactory Epithelium, Hyperplasia, Basal Cell	0	21** (1.0)	44** (1.4)	48** (1.7)
Glands, Dilatation	3 (1.7)	30** (1.2)	48** (1.5)	46** (1.5)
Goblet Cell, Hyperplasia	1 (2.0)	3 (1.7)	7* (1.7)	16** (1.6)
Inflammation, Suppurative	5 (2.4)	9 (1.4)	17** (1.7)	10 (1.6)
Lung	50	50	50	50
Inflammation, Chronic, Focal	4 (1.0)	4 (1.5)	5 (1.6)	14** (1.1)
Alveolar/bronchiolar Adenoma[d]	0	1	0	1
Female				
Nose	50	50	49	49
Olfactory Epithelium, Degeneration	0	50** (1.5)	49** (1.8)	48** (2.0)
Olfactory Epithelium, Hyperplasia, Basal Cell	0	25** (1.0)	42** (1.3)	45** (1.8)
Glands, Dilatation	0	17** (1.3)	38** (1.3)	44** (1.7)
Inflammation, Suppurative	5 (2.4)	12 (1.7)	8 (1.3)	7 (1.6)
Respiratory Epithelium, Adenoma[e]	0	0	0	1
Lung	50	50	50	50
Alveolar Epithelium, Hyperplasia	4 (2.3)	2 (1.5)	3 (1.7)	1 (3.0)
Inflammation, Chronic, Focal	27 (1.3)	22 (1.4)	26 (1.3)	33 (1.2)
Alveolar/bronchiolar Adenoma[f]	0	0	0	2

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[d] Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 14/399 (3.5% ± 4.4%), range 0%-12%
[e] Historical Incidence: 0/397
[f] Historical Incidence: 2/397 (0.5% ± 0.9%), range 0%-2%

cuboidal, or low columner cells, which were occasionally ciliated. Goblet cell hyperplasia was characterized by increased numbers and size of mucus-filled goblet cells, predominantly in the medial septum of level I.

In studies conducted by the NTP, routine sections of the nasal cavity are taken at three levels to allow examination of the major epithelial types in the nasal cavity. The mucosa of the nasal passages in the most rostral level I, taken immediately posterior to the upper incisors, is lined by respiratory epithelium. Level II, taken at the level of the incisive papilla, includes respiratory and olfactory epithelium. The latter covers the mucosa of the dorsal meatus and adjacent dorsal septum. The most posterior level III contains the olfactory portion of the nasal cavity. The lamina propria underlying olfactory epithelium is rich in simple mucus-secreting tubulo-alveolar (Bowman's) glands and unmyelinated nerve bundles of the olfactory nerve. Respiratory epithelium is a simple pseudostratified cuboidal to columner ciliated epithelium containing a few scattered mucin-filled goblet cells. Olfactory epithelium is pseudostratified columnar epithelium composed of sustentacular cells with interposed neuroepithelial sensory cells and a single layer of flattened to cuboidal basal cells.

Lung: Alveolar/bronchiolar adenomas occurred in single males from the 100 and 400 ppm groups and two females from the 400 ppm group. The incidence of this neoplasm in females exceeded the historical incidence for chamber controls. The incidence of focal chronic inflammation in 400 ppm males was significantly greater than in the chamber control group (Tables 14 and A5). Chronic inflammation of the lung was characterized by focal accumulations of (often large and foamy) histiocytes and lesser numbers of lymphocytes and neutrophils associated with necrotic debris, interstitial fibrosis, and hyperplasia of alveolar type II epithelial cells.

Mice

2-Week Study

All 400 ppm mice died by the second day of the study; two male and two female 200 ppm mice also died early (Table 15). Final mean body weights and body weight gains of 100 and 200 ppm males were significantly less than those of the chamber controls, as were the final mean body weights of 25 and 50 ppm males. Lethargy and abnormal breathing were observed in mice exposed to 200 or 400 ppm.

Table 15
Survival and Body Weights of Mice in the 2-Week Inhalation Study of Divinylbenzene-HP

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	5/5	23.3 ± 0.4	28.7 ± 0.2	5.4 ± 0.4	
25	5/5	22.0 ± 0.5	26.5 ± 0.6*	4.5 ± 0.4	92
50	5/5	21.6 ± 0.6	26.2 ± 0.8*	4.6 ± 0.5	91
100	5/5	22.1 ± 0.4	25.7 ± 0.5**	3.5 ± 0.2*	90
200	3/5[c]	22.4 ± 0.7	23.3 ± 1.3**	1.2 ± 1.1**	81
400	0/5[d]	20.4 ± 1.3			
Female					
0	5/5	18.5 ± 0.5	20.9 ± 0.8	2.4 ± 0.6	
25	5/5	20.0 ± 0.4	22.6 ± 0.3	2.7 ± 0.2	108
50	5/5	19.3 ± 0.3	21.8 ± 0.7	2.5 ± 0.9	104
100	5/5	19.0 ± 0.3	21.6 ± 0.5	2.6 ± 0.5	103
200	3/5[e]	19.5 ± 0.4	20.2 ± 0.9	0.5 ± 1.1	97
400	0/5[f]	19.0 ± 0.4			

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
** $P \leq 0.01$
a Number of animals surviving at 2 weeks/number initially in group
b Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
c Day of death: 4, 8
d Day of death: 1, 1, 2, 2, 2
e Day of death: 6, 8
f Day of deaths: 2

Thymus weights of exposed groups of males were significantly less than those of the chamber controls, and relative liver weights of 100 and 200 ppm males were significantly increased (Table G3). Absolute kidney and relative liver weights of exposed groups of females were significantly greater than those of the chamber controls.

Early deaths were associated with liver lesions. Periportal hepatic degeneration with hepatocellular loss and hemorrhage occurred in the 400 ppm group. At 200 ppm, there was centrilobular hepatocellular necrosis with or without mixed inflammatory cell infiltrate, mineralization, and hemosiderin accumulation. Necrosis of respiratory, transitional, and olfactory epithelium and glands in the nose occurred in early death animals.

In 200 ppm mice surviving to the end of the study, hepatocellular karyomegaly (increased nuclear size) accompanied by a general increase in cell size (hypertrophy) was the predominant change. Liver changes corresponded with recorded increases in liver weights in both sexes. Renal tubule necrosis and regeneration with mineralization and granular and proteinaceous casts also occurred in this dose group. Squamous metaplasia of respiratory or transitional epithelium, olfactory epithelial atrophy, and respiratory metaplasia and hyperplasia of Bowman's glands, occurred in the nose. Minimal to mild olfactory epithelial changes were also seen in 25, 50 and 100 ppm animals.

Exposure Concentration Selection Rationale: Based on decreased survival of mice exposed to 400 ppm in the 2-week study, exposure concentrations selected for the 3-month inhalation study in mice were 0, 12.5, 25, 50, 100, and 200 ppm. Although 200 ppm caused some mortality (2/5), this concentration was included in the 3-month study to allow comparison with previous studies of styrene. Styrene caused some mortality in mice; however, survivors developed resistance to hepatotoxicity in spite of continued exposure.

3-Month Study

With the exception of one female, all 200 ppm mice died before the end of the study (Table 16). Final mean body weights and body weight gains of mice exposed to 25 ppm or greater were significantly less than those of the chamber controls. During the first 3 weeks of the study, lethargy or hypoactivity were observed in the higher exposure concentration groups.

Table 16
Survival and Body Weights of Mice in the 3-Month Inhalation Study of Divinylbenzene-HP

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	10/10	22.6 ± 0.3	36.8 ± 0.5	14.2 ± 0.4	
12.5	10/10	22.9 ± 0.2	37.0 ± 0.7	14.1 ± 0.7	100
25	10/10	22.7 ± 0.4	33.2 ± 0.9**	10.5 ± 0.6**	90
50	10/10	22.8 ± 0.4	31.8 ± 0.8**	8.9 ± 0.5**	86
100	10/10	22.5 ± 0.3	31.3 ± 0.4**	8.8 ± 0.3**	85
200	0/10[c]				
Female					
0	10/10	19.1 ± 0.2	31.1 ± 0.8	12.0 ± 0.8	
12.5	10/10	19.6 ± 0.3	31.9 ± 1.2	12.3 ± 1.0	103
25	10/10	19.3 ± 0.4	28.5 ± 0.4**	9.1 ± 0.3**	91
50	10/10	19.6 ± 0.2	28.3 ± 0.4**	8.8 ± 0.4**	91
100	10/10	19.4 ± 0.2	28.1 ± 0.3**	8.7 ± 0.3**	90
200	1/10[d]	19.7 ± 0.2	26.8	6.2	86

** Significantly different ($P \leq 0.01$) from the chamber control group by Williams' test
[a] Number of animals surviving at 3 months/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Week of deaths: 1
[d] Week of death: 1, 1, 1, 1, 1, 2, 2, 3, 3

The hematology data for mice in the 3-month toxicity study of divinylbenzene are listed in Tables 17 and F2. There was small (< 15%) decrease in the erythron, characterized by decreases in hemoglobin concentrations, hematocrit values, and erythrocyte counts in females exposed to 25 ppm or greater; the decrease was less than 5% in all but the 200 ppm group. This change was associated with decreases (20% to 30%) in reticulocyte counts in the 50, 100, and 200 ppm groups and could suggest a minimal erythropoietic suppression for this species.

In male mice exposed to 25 ppm or greater, the absolute weights of the heart, kidney, and liver were significantly decreased, and the relative weights of the lung and testis were generally increased (Table G4). Liver weights and absolute thymus weights were significantly decreased in 50 and 100 ppm females. In addition, absolute heart weights were significantly decreased in 25 ppm or greater females. These organ weight changes were considered to reflect the body weight changes noted above. There were no significant differences between exposed and chamber control groups in reproductive tissue evaluations in males or vaginal cytology parameters in females (Tables H3 and H4).

TABLE 17
Selected Hematology Data for Female Mice in the 3-Month Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	12.5 ppm	25 ppm	50 ppm	100 ppm	200 ppm
n	10	10	10	10	10	1[b]
Automated hematocrit (%)	51.0 ± 0.4	50.3 ± 0.4	50.0 ± 0.2	49.5 ± 0.4*	49.3 ± 0.3**	44.6
Manual hematocrit (%)	51.0 ± 0.3	50.8 ± 0.3	50.0 ± 0.2*	49.6 ± 0.5*	49.3 ± 0.3**	44.5
Hemoglobin (g/dL)	16.5 ± 0.1	16.4 ± 0.1	16.2 ± 0.1**	16.0 ± 0.1**	16.0 ± 0.1**	14.2
Erythrocytes (10^6/µL)	10.34 ± 0.08	10.05 ± 0.07*	10.10 ± 0.03*	10.06 ± 0.07*	9.91 ± 0.07**	9.01
Reticulocytes (10^6/µL)	0.25 ± 0.02	0.24 ± 0.01	0.21 ± 0.01	0.20 ± 0.01*	0.20 ± 0.01*	0.17
Leukocytes (10^3/µL)	3.42 ± 0.25	3.88 ± 0.16	3.12 ± 0.21	3.24 ± 0.19	2.91 ± 0.31	1.50
Lymphocytes (10^3/µL)	3.00 ± 0.24	3.29 ± 0.14	2.80 ± 0.19	2.81 ± 0.14	2.40 ± 0.19	1.05

* Significantly different (P≤0.05) from the chamber control group by Dunn's or Shirley's test
** P≤0.01
a Mean ± standard error. Statistical tests were performed on unrounded data.
b No standard error was calculated or pairwise test performed for this exposure group because only single measurements were available.

Although no gross lesions were observed that could be attributed to exposure to divinylbenzene-HP, microscopic lesions occurred in several tissues of exposed mice (Table 18).

Microscopic lesions varied according to exposure levels and length of survival and were similar to those seen in the 2-week study. Mice in the 200 ppm groups that died early had significantly increased incidences of hepatocellular centrilobular necrosis and mineralization, renal tubule necrosis with mineralization, and granular and protein casts. Increased incidences of necrosis involving nasal cavity lateral walls, olfactory epithelium, and glands occurred in both sexes, with resultant atrophy of olfactory epithelium and glands in females. A lower number of animals had necrotic or degenerative changes of the upper respiratory tract. All other changes were considered to be secondary to stress and/or the moribund condition of the animals and not directly associated with exposure to divinylbenzene-HP.

Exposure-related changes in mice of both sexes surviving to the end of the study were restricted to the nose. Olfactory epithelial necrosis occurred in all animals from the 50 and 100 ppm exposure groups, and the incidence was greater in both sexes (reaching statistical significance in males) at 25 ppm. Olfactory epithelial atrophy and degeneration was characterized by disorganization and decreased thickness of neuroepithelium. Bowman’s gland hyperplasia was characterized by increased numbers of cells lining the glands. Olfactory epithelium atrophy, degeneration, inflammation, and (regenerative) hyperplasia of Bowman’s glands occurred in the majority of animals from all exposure groups. Hyaline degeneration of epithelium consisted of epithelial cytoplasmic distension with amorphous, strongly eosinophilic material. Hyaline degeneration of the respiratory epithelium had a greater incidence and severity at lower exposure concentrations and was increased in both sexes at 12.5 ppm and in females exposed to 50 and 100 ppm.

Exposure Concentration Selection Rationale: Based on decreased survival and severity of liver, kidney, and nasal lesions in mice exposed to 200 ppm divinylbenzene-HP in the 3-month study, exposure concentrations selected for the 2-year inhalation study in mice were 0, 10, 30, and 100 ppm.

TABLE 18
Incidences of Selected Nonneoplastic Lesions in Mice in the 3-Month Inhalation Study of Divinylbenzene-HP

	Chamber Control	12.5 ppm	25 ppm	50 ppm	100 ppm	200 ppm
Male						
Liver[a]	10	0	0	0	10	10
Mineralization[b]	0				0	6** (2.5)[c]
Centrilobular, Necrosis	0				0	10** (2.8)
Larynx	10	1	0	0	10	10
Degeneration, Acute	0	0			0	3 (1.0)
Lung	10	0	0	0	10	10
Bronchiole, Necrosis	0				0	4* (1.0)
Bronchiole, Epithelium, Hyperplasia	0				0	1 (1.0)
Nose	10	10	10	10	10	10
Infiltration Cellular, Mixed Cell	0	9** (1.0)	10** (1.0)	10** (1.0)	10**(1.0)	0
Glands, Atrophy	0	0	0	0	10**(2.6)	0
Glands, Hyperplasia	0	9** (2.1)	10** (3.5)	10** (2.7)	10**(1.9)	0
Glands, Necrosis	0	0	0	0	0	10** (4.0)
Lateral Wall, Necrosis	0	0	0	0	0	9** (2.0)
Olfactory Epithelium, Atrophy	0	10** (1.4)	10** (2.0)	10** (2.0)	10** (2.0)	0
Olfactory Epithelium, Degeneration, Hyaline	0	7** (1.4)	10** (2.0)	10** (2.0)	9** (2.0)	0
Olfactory Epithelium, Necrosis	0	0	4* (1.0)	10** (1.1)	10** (1.9)	10** (3.9)
Respiratory Epithelium, Degeneration, Hyaline	0	8** (1.4)	1 (1.0)	0	1 (2.0)	0
Trachea	9	0	0	0	10	10
Degeneration	0				0	2 (1.0)
Kidney	10	2	1	10	10	9
Casts Granular	0	0	0	0	0	8** (2.9)
Casts Protein	0	0	1 (1.0)	0	0	8** (3.4)
Mineralization	0	0	0	0	0	8** (2.8)
Renal Tubule, Necrosis	0	0	0	0	0	9** (4.0)
Renal Tubule, Regeneration	0	2* (1.0)	0	0	1 (1.0)	1 (1.0)

Table 18
Incidences of Selected Nonneoplastic Lesions in Mice in the 3-Month Inhalation Study of Divinylbenzene-HP

	Chamber Control	12.5 ppm	25 ppm	50 ppm	100 ppm	200 ppm
Female						
Liver	10	0	0	0	10	10
Infiltration Cellular, Histiocyte	0				0	7** (1.6)
Mineralization	0				0	7** (2.1)
Pigmentation	0				0	4* (1.0)
Centrilobular, Hypertrophy	0				0	4* (1.8)
Centrilobular, Necrosis	0				0	9** (2.4)
Larynx	10	0	0	0	10	10
Degeneration	0				0	2 (1.0)
Lung	10	0	0	0	10	10
Bronchiole, Necrosis	0				0	2 (1.0)
Nose	10	10	10	10	10	10
Infiltration Cellular, Mixed Cell	0	9** (1.0)	10** (1.0)	10** (1.0)	10** (1.0)	5* (1.0)
Glands, Atrophy	0	0	0	0	7** (1.1)	5* (3.4)
Glands, Hyperplasia	0	10** (1.3)	10** (3.2)	10** (3.0)	10** (2.3)	3 (1.3)
Glands, Necrosis	0	0	0	0	0	6** (3.2)
Lateral Wall, Necrosis	0	0	0	0	0	7** (1.7)
Olfactory Epithelium, Atrophy	0	10** (1.3)	10** (2.1)	10** (2.0)	10** (1.9)	5* (2.8)
Olfactory Epithelium, Degeneration, Hyaline	0	10** (1.3)	10** (2.0)	10** (2.8)	10** (2.6)	1 (2.0)
Olfactory Epithelium, Necrosis	0	0	3 (1.0)	10** (1.1)	10** (1.5)	10** (3.4)
Respiratory Epithelium, Degeneration, Hyaline	0	10** (2.0)*	6** (1.2)	6** (1.2)	1 (1.0)	0
Trachea	10	0	0	0	10	10
Degeneration	0				0	2 (1.0)
Kidney	10	0	2	10	10	10
Casts Granular	0		0	0	0	8** (1.8)
Casts Protein	0		1 (1.0)	0	0	7** (2.3)
Mineralization	0		0	0	0	5* (2.4)
Renal Tubule, Necrosis	0		0	0	0	9** (3.3)

* Significantly different (P≤0.05) from the chamber control group by the Fisher exact test
** P≤0.01
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

2-Year Study

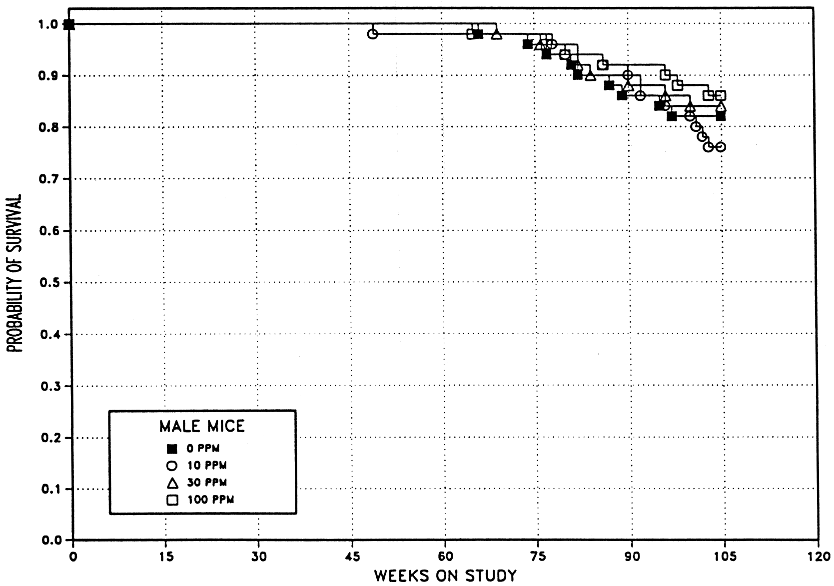
Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 19 and in the Kaplan-Meier survival curves (Figure 5). Survival of all exposed groups of mice was similar to that of the chamber controls.

Table 19
Survival of Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	7	6	5	4
Natural deaths	2	6	3	3
Animals surviving to study termination	41	38	42	43
Percent probability of survival at end of study[a]	82	76	84	86
Mean survival (days)[b]	702	703	707	711
Survival analysis[c]	P=0.433N	P=0.687	P=0.966N	P=0.750N
Female				
Animals initially in study	50	50	50	50
Accidental death[d]	0	0	1	0
Moribund	11	12	8	7
Natural deaths	6	3	3	1
Animals surviving to study termination	33	35	38	42
Percent probability of survival at end of study	66	70	78	84
Mean survival (days)	681	700	689	705
Survival analysis	P=0.050N	P=0.729N	P=0.293N	P=0.053N

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] The result of the life table trend test (Tarone, 1975) is in the chamber control column, and the results of the life table pairwise comparisons (Cox, 1972) with the chamber controls are in the exposed group columns. A negative trend or lower mortality in an exposed group is indicated by **N**.
[d] Censored from survival analyses



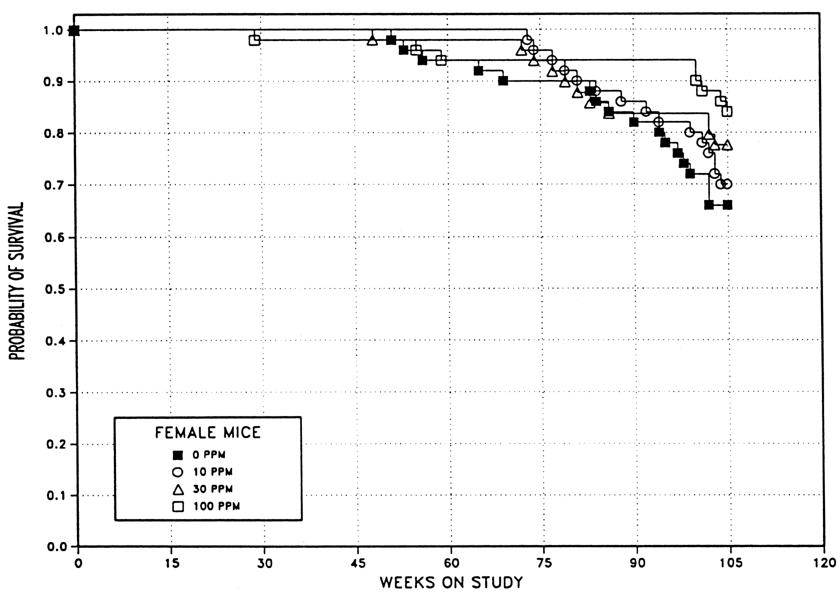


FIGURE 5
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Divinylbenzene-HP by Inhalation for 2 Years

Body Weights and Clinical Findings

Mean body weights of 30 and 100 ppm males were generally less than those of the chamber controls throughout the first year of the study; those of 100 ppm males remained less than those of the chamber controls at the end of the study (Figure 6; Tables 20 and 21). Mean body weights of 10 ppm females were less than those of the chamber controls during the middle third of the study. Mean body weights of 30 ppm females were less than those of the chamber controls from week 21 to nearly the end of the study. Mean body weights of 100 ppm females were less than those of the chamber controls during the entire 2-year study. No clinical findings related to chemical exposure were observed.

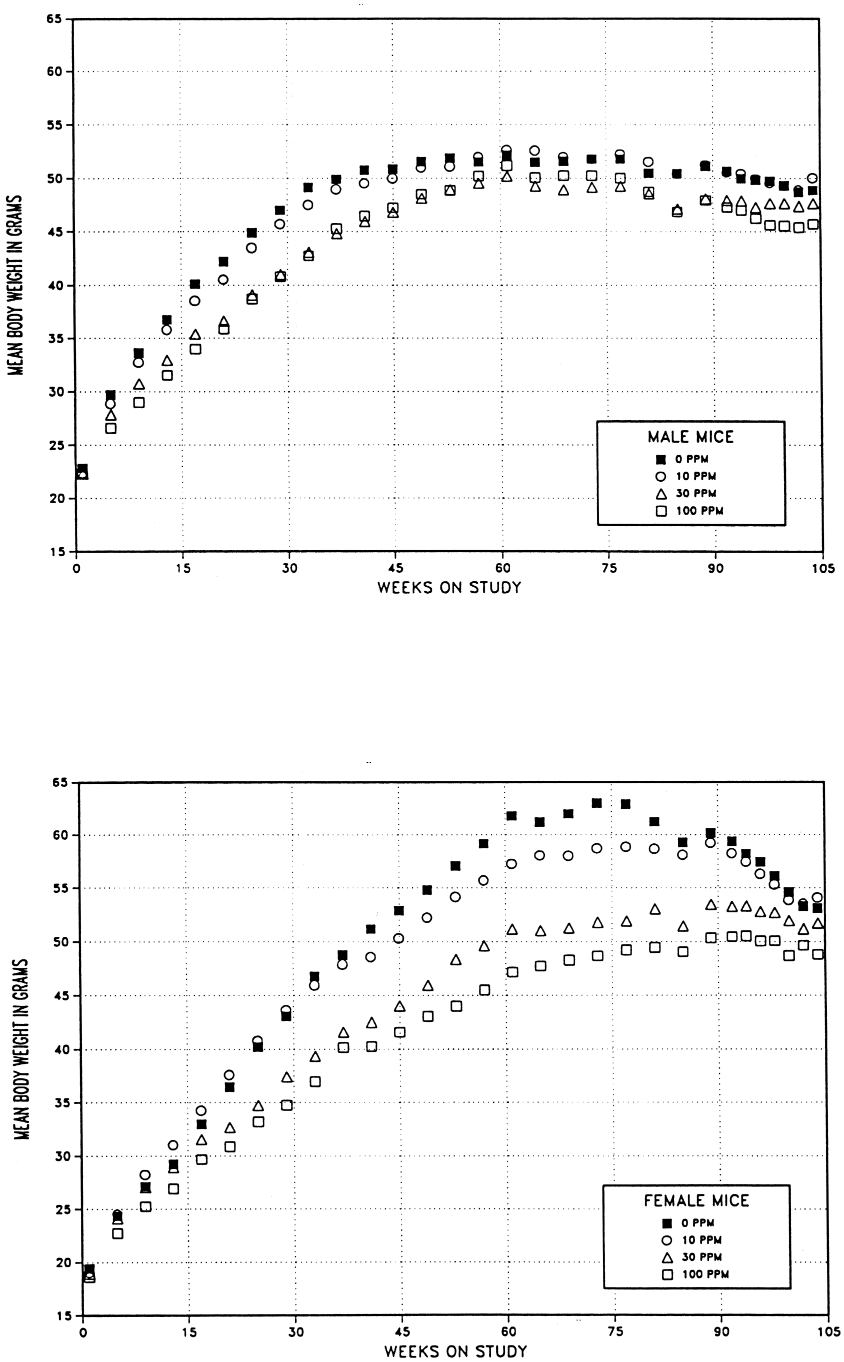


FIGURE 6
Growth Curves for Male and Female Mice
Exposed to Divinylbenzene-HP by Inhalation for 2 Years

Table 20
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

Weeks on Study	Chamber Control		10 ppm			30 ppm			100 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	22.9	50	22.4	98	50	22.3	97	50	22.4	98	50
5	29.7	50	28.8	97	50	27.8	94	50	26.6	90	50
9	33.6	50	32.7	97	50	30.8	92	50	29.0	86	50
13	36.8	50	35.8	97	50	33.0	90	50	31.6	86	50
17	40.1	50	38.5	96	50	35.4	88	50	34.0	85	50
21	42.2	50	40.5	96	50	36.6	87	50	35.9	85	50
25	44.9	50	43.5	97	50	39.1	87	50	38.7	86	50
29	47.0	50	45.7	97	50	41.0	87	50	40.8	87	50
33	49.1	50	47.5	97	50	43.1	88	50	42.8	87	50
37	49.9	50	49.0	98	50	44.8	90	50	45.3	91	50
41	50.8	50	49.5	97	50	46.0	91	50	46.4	91	50
45	50.9	50	50.0	98	50	46.8	92	50	47.2	93	50
49	51.6	50	51.0	99	49	48.1	93	50	48.5	94	50
53	51.9	50	51.1	99	49	48.9	94	50	48.8	94	50
57	51.6	50	52.0	101	49	49.5	96	50	50.2	97	50
61	52.2	50	52.7	101	49	50.2	96	50	51.2	98	50
65	51.5	50	52.6	102	49	49.2	96	50	50.1	97	50
69	51.6	49	52.0	101	49	48.9	95	49	50.3	98	49
73	51.8	49	51.8	100	49	49.1	95	49	50.3	97	49
77	51.8	48	52.3	101	49	49.2	95	48	50.0	97	48
81	50.5	47	51.6	102	47	48.5	96	48	48.7	96	47
85	50.4	45	50.4	100	47	47.1	94	45	46.9	93	47
89	51.2	44	51.3	100	46	48.1	94	45	47.9	94	46
92	50.7	43	50.5	100	44	47.9	95	44	47.3	93	46
94	50.0	43	50.4	101	43	47.9	96	44	47.0	94	46
96	49.8	42	50.0	100	43	47.3	95	44	46.2	93	45
98	49.7	41	49.5	100	42	47.6	96	43	45.6	92	45
100	49.3	41	49.3	100	42	47.6	97	42	45.6	93	44
102	48.7	41	48.9	100	40	47.4	97	42	45.4	93	44
104	48.9	41	50.0	102	38	47.7	98	42	45.7	94	43
Mean for weeks											
1-13	30.8		29.9	97		28.5	93		27.4	89	
14-52	47.4		46.1	97		42.3	89		42.2	89	
53-104	50.7		51.0	101		48.4	95		48.1	95	

TABLE 21
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

Weeks on Study	Chamber Control		10 ppm			30 ppm			100 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	19.4	50	19.0	98	50	18.9	97	50	18.6	96	50
5	24.4	50	24.5	100	50	24.1	99	50	22.7	93	50
9	27.1	50	28.2	104	50	27.0	100	50	25.3	93	50
13	29.2	50	31.0	106	50	28.9	99	50	26.9	92	50
17	33.0	50	34.2	104	50	31.6	96	50	29.7	90	50
21	36.4	50	37.6	103	50	32.7	90	50	30.9	85	50
25	40.2	50	40.8	102	50	34.7	86	50	33.2	83	50
29	43.1	50	43.6	101	50	37.4	87	50	34.8	81	50
33	46.8	50	45.9	98	50	39.4	84	50	37.0	79	49
37	48.8	50	47.9	98	50	41.6	85	50	40.2	82	49
41	51.2	50	48.6	95	50	42.5	83	50	40.3	79	49
45	52.9	50	50.3	95	50	44.0	83	50	41.6	79	49
49	54.8	50	52.2	95	50	46.0	84	49	43.1	79	49
53	57.1	48	54.2	95	50	48.4	85	48	44.0	77	49
57	59.2	47	55.7	94	50	49.6	84	48	45.5	77	48
61	61.8	47	57.2	93	50	51.2	83	48	47.2	76	47
65	61.2	46	58.0	95	50	51.0	83	48	47.7	78	47
69	62.0	45	58.0	94	50	51.3	83	48	48.3	78	47
73	63.0	45	58.7	93	49	51.8	82	47	48.7	77	47
77	62.9	45	58.8	94	48	51.9	83	46	49.2	78	47
81	61.2	45	58.7	96	46	53.1	87	44	49.5	81	47
85	59.3	43	58.1	98	44	51.5	87	42	49.1	83	47
89	60.2	42	59.2	98	43	53.5	89	41	50.3	84	47
92	59.4	41	58.2	98	42	53.3	90	41	50.5	85	47
94	58.2	41	57.5	99	42	53.3	92	41	50.5	87	47
96	57.5	39	56.3	98	41	52.8	92	41	50.1	87	47
98	56.1	37	55.3	99	41	52.7	94	41	50.1	89	47
100	54.6	36	53.9	99	40	52.0	95	41	48.7	89	47
102	53.3	34	53.5	100	38	51.2	96	40	49.7	93	44
104	53.1	33	54.1	102	36	51.7	97	38	48.8	92	44
Mean for weeks											
1-13	25.0		25.7	103		24.7	99		23.4	94	
14-52	45.2		44.6	99		38.9	86		36.8	82	
53-104	58.8		56.8	97		51.8	88		48.7	83	

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the lung, nose, eye, and liver. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Lung: The incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) in 100 ppm males were slightly greater than the concurrent and historical chamber control incidences (Tables 22, C3 and C4). However, decreased incidences were seen in the 10 and 30 ppm groups when compared with concurrent and historical chamber controls. In view of the lack of dose response, alveolar/bronchiolar adenoma and/or carcinoma in male mice were not considered to be associated with exposure to divinylbenzene. The incidence and severity of alveolar epithelial hyperplasia were higher in all exposed groups of males when compared with controls but the average severity of the lesion did not increase with exposure concentration (Tables 22 and C5).

The incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) in all exposed groups of females were generally, although not significantly, higher that the concurrent and historical control incidences (Tables 22, D3, and D4). In addition, there was a greater incidence and/or severity of alveolar epithelial hyperplasia in 30 and 100 ppm females when compared with chamber controls (Tables 22 and D5). Therefore, there was a possible association between divinylbenzene-HP exposure and the occurrence of alveolar/bronchiolar adenoma or carcinoma in female mice. In both sexes, the incidences of minimal to mild atypical bronchiolar epithelial hyperplasia were significantly increased and, in general, the average group severity increased with increasing exposure concentrations. Incidences of alveolar histiocytic cellular infiltration increased with increasing exposure concentration in females, and the increase was significant in the 100 ppm group.

Table 22
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Male				
Number Examined Microscopically	49	49	49	49
Bronchiole, Hyperplasia, Atypical[a]	0	38** (1.1)[b]	46** (1.8)	46** (2.0)
Alveolar Epithelium, Hyperplasia	1 (1.0)	5 (3.2)	5 (2.0)	7* (2.0)
Alveolus, Infiltration Cellular, Histiocyte	2 (1.5)	4 (1.0)	5 (1.0)	1 (1.0)
Alveolar/bronchiolar Adenoma (includes multiple)[c]	12	6	6	15
Alveolar/bronchiolar Carcinoma (includes multiple)	5	4	3	9
Alveolar/bronchiolar Adenoma or Carcinoma[d]				
Overall Rate[e]	16/49 (33%)	10/49 (20%)	8/49 (16%)	20/49 (41%)
Adjusted Rate[f]	34.7%	21.9%	17.4%	42.0%
Terminal Rate[g]	15/41 (37%)	9/38 (24%)	8/42 (19%)	17/43 (40%)
First Incidence (days)	536	711	729 (T)	598
Poly-3 test[h]	P=0.053	P=0.128N	P=0.046N	P=0.306
Female				
Number Examined Microscopically	50	50	50	49
Bronchiole, Hyperplasia, Atypical	0	39** (1.3)	45** (1.8)	48** (2.1)
Alveolar Epithelium, Hyperplasia	4 (1.8)	3 (1.7)	4 (2.3)	8 (2.5)
Alveolus, Infiltration Cellular, Histiocyte	3 (1.0)	6 (1.0)	9 (1.1)	17** (1.2)
Alveolar/bronchiolar Adenoma (includes multiple)[i]	4	9	4	8
Alveolar/bronchiolar Carcinoma (includes multiple)	2	5	4	5
Alveolar/bronchiolar Adenoma or Carcinoma[j]				
Overall Rate	6/50 (12%)	12/50 (24%)	8/50 (16%)	13/49 (27%)
Adjusted Rate	14.1%	26.7%	17.9%	27.7%
Terminal Rate	6/33 (18%)	11/35 (31%)	6/38 (16%)	11/42 (26%)
First Incidence (days)	731 (T)	719	536	697
Poly-3 test	P=0.161	P=0.114	P=0.421	P=0.092

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test
** $P \leq 0.01$
(T) Terminal sacrifice
a Number of animals with lesion
b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
c Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 74/349 (21.2% ± 5.8%), range 12%-26%
d Historical incidence: 115/349 (33.0% ± 6.0%), range 26%-44%
e Number of animals with neoplasm per number of animals with lung examined microscopically
f Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
g Observed incidence at terminal kill
h Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposed group is indicated by **N**.
i Historical incidence: 17/349 (4.9 % ± 2.5%), range 2%-8%
j Historical incidence: 27/349 (7.8% ± 4.3%), range 2%-14%

Alveolar epithelial hyperplasia is considered to represent a morphological continuum with alveolar/bronchiolar neoplasms, and it consisted of focal thickening of alveolar septae by increased numbers of prominent, cuboidal, type II pneumocytes, with maintenance of normal alveolar architecture. Alveolar/bronchiolar adenomas consisted of well-demarcated hypercellular masses distorting normal septal architecture and characterized by well-differentiated cuboidal cells forming papillary projections into alveolar or bronchiolar lumina. Alveolar/bronchiolar carcinomas were more irregular, hypercellular masses distorting normal architecture, with variable peripheral compression and invasion. Component cells were pleomorphic, polygonal to columnar, arranged in solid sheets or forming papillary projections into the alveolar or bronchiolar lumina. Regionally extensive bronchiolar atypical epithelial hyperplasia occurred within bronchioles and extended to terminal bronchioles characterized by foci of enlarged karyomegalic cells with increased cytoplasmic and nuclear basophilia in single and multiple layers with variable loss of cellular orientation and occasionally formed outfolding, intraluminal papillary projections. This change was morphologically consistent with that seen in the later stages of airway epithelium regeneration (Dixon *et al.*, 1999). It has also been described as a putative preneoplastic lesion in the lungs of mice exposed to styrene. It is unclear whether it represents a preneoplastic change in this study. It was distinct in location and morphology from alveolar epithelial hyperplasia.

Nose: A single incidence of neuroblastoma of the olfactory epithelium occurred in a 100 ppm female (Tables 23 and D1). Multifocally expanding the lamina propria and distorting Bowman's glands of the nasal septum and turbinates (Section 3) were clusters and cords of hyperchromatic cells. Component cells had ovoid to irregular nuclei with prominent nucleoli. Cytoplasm was scant and amphophilic. There was moderate anisokariosis, plentiful mitoses, and admixed karryorhectic debris. In one area, a small, poorly-circumscribed mass was composed of similar cells, which occasionally formed rosettes and extended to, but did not invade, turbinate bone.

Olfactory neuroblastomas are an extremely rare neoplasm in mice, with no recorded cases in historical background data (all routes of administration; 0/1,555). They arise within areas of atypical epithelial hyperplasia and progress to olfactory neuroblastoma without a preceding benign neoplastic lesion. Olfactory neuroblastomas are generally

Table 23
Incidences of Neoplasms and Nonneoplastic Lesions of the Nose in Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Male				
Number Examined Microscopically	50	50	49	50
Inflammation, Suppurative[a]	3 (1.0)[b]	47** (1.4)	49** (1.9)	49** (1.9)
Glands, Respiratory Epithelium, Metaplasia	12 (1.0)	50** (2.9)	49** (4.0)	50** (3.9)
Olfactory Epithelium, Respiratory Epithelium, Metaplasia	1 (2.0)	50** (3.1)	49** (4.0)	50** (3.9)
Olfactory Epithelium, Degeneration, Hyaline	5 (1.0)	50** (1.9)	48** (1.8)	11 (1.1)
Female				
Number Examined Microscopically	50	50	50	49
Inflammation, Suppurative	1 (1.0)	50** (1.7)	49** (2.0)	49** (2.4)
Glands, Respiratory Epithelium, Metaplasia	3 (1.0)	50** (3.1)	50** (3.6)	49** (4.0)
Olfactory Epithelium, Respiratory Epithelium, Metaplasia	0	50** (3.1)	50** (3.9)	49** (3.9)
Olfactory Epithelium, Degeneration, Hyaline	2 (1.5)	50** (2.4)	40** (1.8)	8 (1.6)
Olfactory Epithelium, Neuroblastoma[c]	0	0	0	1

** Significantly different ($P \leq 0.01$) from the chamber control group by the Poly-3 test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year inhalation studies with chamber control groups: 0/348

destructive and highly invasive, often invading the brain by extension through the ethmoid bone. This was a very marginal lesion, barely meeting the criteria for neoplasia. No cases of atypical hyperplasia were seen in males or females from any of the exposure groups.

Incidences of suppurative inflammation and respiratory epithelial metaplasia of Bowman's glands and olfactory epithelium were significantly increased in all exposed groups of mice, and the severities of these lesions tended to increase with increasing exposure concentration (Tables 23, C5, and D5). Incidences of hyaline degeneration of the olfactory epithelium were significantly increased in 10 and 30 ppm males and females. These lesions are consistent with ongoing degeneration and regeneration of olfactory epithelium and associated glands.

Microscopically, suppurative inflammation consisted of accumulations of neutrophils and proteinaceous fluid in the nasal lumen, with occasional extension into the lumina of Bowman's glands. Respiratory metaplasia of the olfactory epithelium was characterized by replacement of normal olfactory epithelium in Level II and, to a greater extent, Level III by ciliated respiratory epithelium. Increasing severity corresponded to extension of metaplastic epithelium from the dorsal meatus to involve the turbinates. Respiratory metaplasia of Bowman's glands was diagnosed when there was extension of this ciliated epithelium (Plates 3 and 4) into, and replacement of subjacent Bowman's gland epithelium with a corresponding decrease in lumenal area. Hyaline degeneration of olfactory epithelium, usually involving the lateral walls of ethmoid turbinates in Level III, consisted of areas of epithelial cytoplasmic distension with amorphous, strongly eosinophilic material.

Eye: The incidence of minimal corneal mineralization was significantly increased in 100 ppm females (chamber control, 0/50; 10 ppm, 0/50; 30 ppm, 0/50; 100 ppm, 6/49; Table D5); minimal corneal mineralization also occurred in two 100 ppm males (0/49, 0/47, 0/47, 2/50; Table C5). Histologically, this change was characterized by focal mineralization and cleft formation in the stroma with atrophy of overlying epithelium. There was no evidence of concurrent ocular disease, and harderian gland adenoma occurred in only one of the 100 ppm females that had corneal mineralization (data not shown).

Liver: In general, exposure of mice to divinylbenzene-HP was associated with negative trends in the incidences of hepatocellular proliferative lesions (Tables 24, C3, and D3). Incidences of hepatocellular adenoma were significantly decreased in 30 and 100 ppm males, and the incidences were below the historical range in chamber controls. Incidences of hepatocellular adenoma or carcinoma (combined) were at or below the lower end of the historical range in all exposed groups of males, and the incidence in the 30 ppm group was significantly decreased. Hepatoblastoma occurred in two 30 ppm males; this lesion has not been observed in historical chamber control male mice. Incidences of hepatocellular adenoma and adenoma or carcinoma (combined) were significantly decreased in all exposed groups of females, and the incidences were at or below the lower end of the historical control ranges for chamber control female mice (Tables 24 and D3).

TABLE 24
Incidences of Neoplasms of the Liver in Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Male				
Number Examined Microscopically	50	50	50	50
Hepatocellular Adenoma, Multiple[a]	12	5*	2**	1**
Hepatocellular Adenoma (includes multiple)[b]				
Overall rate[c]	22/50 (44%)	17/50 (34%)	12/50 (24%)	12/50 (24%)
Adjusted rate[d]	47.1%	35.8%	25.2%	25.4%
Terminal rate[e]	20/41 (49%)	13/38 (34%)	9/42 (21%)	12/43 (28%)
First incidence (days)	456	543	526	729 (T)
Poly-3 test[f]	P=0.039N	P=0.181N	P=0.020N	P=0.022N
Hepatocellular Carcinoma (includes multiple)	13	11	9	10
Hepatocellular Adenoma or Carcinoma[g]				
Overall rate	30/50 (60%)	26/50 (52%)	20/50 (40%)	22/50 (44%)
Adjusted rate	61.8%	53.2%	40.0%	46.0%
Terminal rate	24/41 (59%)	17/38 (45%)	12/42 (29%)	21/43 (49%)
First incidence (days)	456	543	479	533
Poly-3 test	P=0.131N	P=0.256N	P=0.023N	P=0.086N
Hepatoblastoma[h]	0	0	2	0
Female				
Number Examined Microscopically	49	50	50	50
Hepatocellular Adenoma (includes multiple)[i]				
Overall rate	17/49 (35%)	7/50 (14%)	6/50 (12%)	5/50 (10%)
Adjusted rate	39.7%	15.4%	13.6%	10.7%
Terminal rate	13/33 (39%)	5/35 (14%)	5/38 (13%)	5/42 (12%)
First incidence (days)	625	537	709	731 (T)
Poly-3 test	P=0.010N	P=0.008N	P=0.004N	P<0.001N
Hepatocellular Carcinoma (includes multiple)	5	4	3	2
Hepatocellular Adenoma or Carcinoma[j]				
Overall rate	19/49 (39%)	10/50 (20%)	8/50 (16%)	7/50 (14%)
Adjusted rate	43.9%	21.9%	17.9%	14.9%
Terminal rate	14/33 (42%)	7/35 (20%)	6/38 (16%)	7/42 (17%)
First incidence (days)	586	537	501	731 (T)
Poly-3 test	P=0.012N	P=0.021N	P=0.006N	P=0.002N

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test
** $P \leq 0.01$
(T) Terminal sacrifice
a Number of animals with lesion
b Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 134/350 (38.3% ± 6.3%), range 30%-46%
c Number of animals with neoplasm per number of animals with liver examined microscopically
d Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
e Observed incidence at terminal kill
f Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
g Historical incidence: 146/350 (56.0% ± 6.2%), range 50%-68%
h Historical incidence: 0/350
i Historical incidence: 78/347 (22.5% ± 8.1%), range 12%-35%
j Historical incidence: 108/347 (31.1% ± 6.8%), range 22%-39%

Decreases in body weight were insufficient to account for the decreased incidence of hepatocellular neoplasms in all exposed groups of females, according to data reported by Haseman *et al*. (1997). The reason for this decrease is, therefore, unclear.

Genetic Toxicology

Divinylbenzene was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537 or the *Escherichia coli* tester strain WPM uvrA when tested with and without induced hamster or rat liver S9 in any of three independently conducted assays (Tables E1 and E2; Zeiger *et al.*, 1987). The highest concentration tested at one laboratory was 100 µg/plate; the other two laboratories tested higher concentrations, up to 1,000 µg/plate. It should be considered that inadequate exposure of the tester strains may have occurred, as incubation with this volatile compound was not carried out within the closed environment of a desiccator. No increases in the frequencies of micronucleated normochromatic erythrocytes or alterations in the percentage of polychromatic erythrocytes were seen in peripheral blood of male or female $B6C3F_1$ mice exposed to divinylbenzene-HP by inhalation (up to 200 ppm) for 3 months (Table E2).

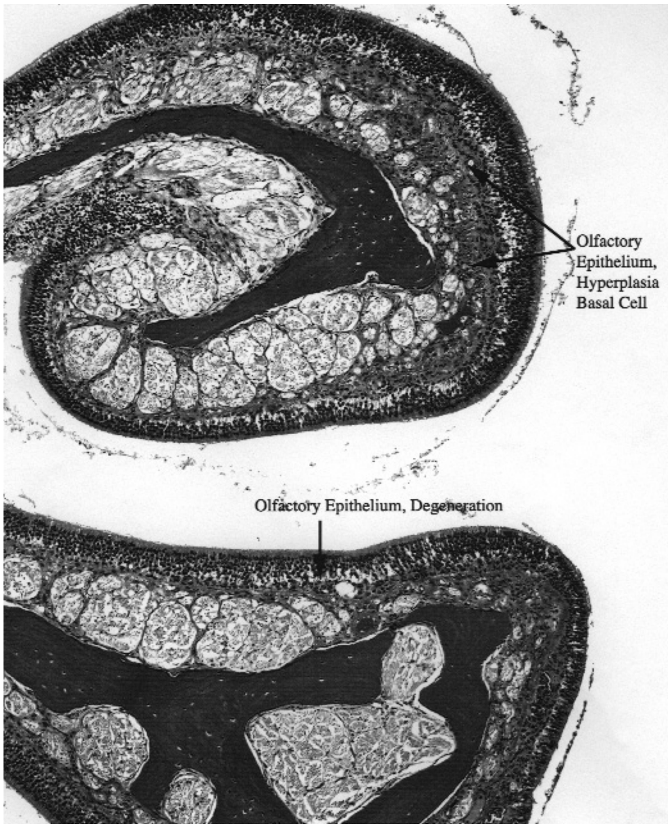


Plate 1
Marked olfactory epithelial degeneration with mild basal cell hyperplasia involving the nasal turbinates of a female F344/N rat exposed to 400 ppm divinylbenzene-HP for 2 years. H&E × 10

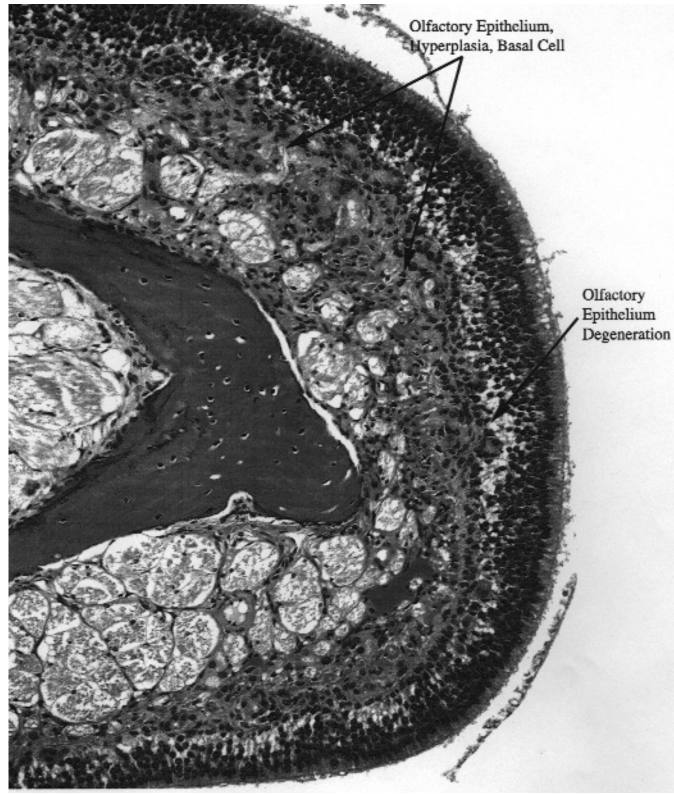


Plate 2
Higher magnification of Plate 1. Note olfactory epithelial degeneration characterized by loss and disorganization of neuroepithelial cells and increased numbers of basal cells. H&E × 20

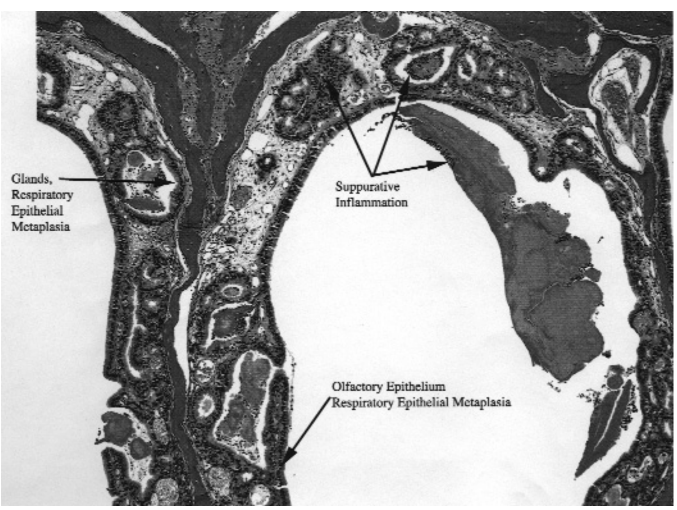


Plate 3
Marked respiratory epithelial metaplasia involving glands and olfactory epithelium and suppurative exudate in the nose of a female B6C3F$_1$ mouse exposed to 100 ppm divinylbenzene-HP for 2 years. H&E × 10

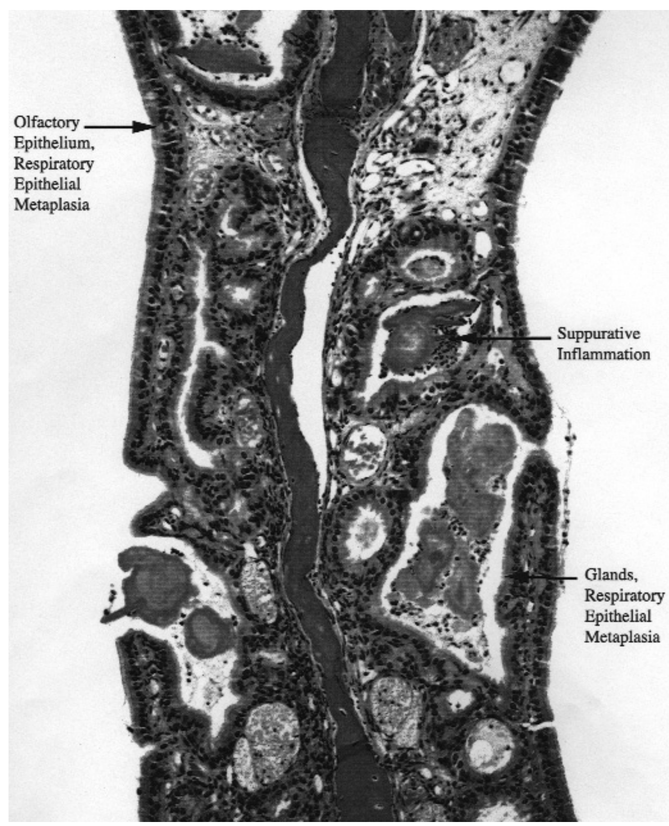


Plate 4
Higher magnification of Plate 3. Note replacement of olfactory and glandular epithelium with ciliated respiratory epithelium (respiratory metaplasia). The mucosa is mildly inflamed, and inflammatory exudate variably fills glandular lumina. H&E × 20

DISCUSSION AND CONCLUSIONS

Divinylbenzene was nominated by the National Cancer Institute for carcinogenesis studies based upon the potential for worker exposure and the structural similarity of divinylbenzene to styrene, a possible human carcinogen (Group 2B) (IARC, 2002). Styrene is metabolized by cytochrome P450, principally CYPE1 and CYP2F2 (Nakajima *et al*., 1994; Carlson, 1997; Green *et al.*, 2001a), to styrene-7,8-epoxide, a direct-acting carcinogen (IARC, 1987), and divinylbenzene is likely oxidized to an epoxide and/or diepoxide by this same pathway. Because divinylbenzene has two reactive vinyl substituents and can be metabolized to a diepoxide, it may be more reactive and toxic than styrene.

In the 2-week inhalation studies, rats and mice were exposed to 25, 50, 100, 200, or 400 ppm divinylbenzene-high purity (divinylbenzene-HP). These exposure concentrations were selected based on the maximum attainable concentration that could be generated without aerosolization of 480 ppm. In the rat study, there were no deaths and only a modest decrease in body weights (10% and 8%, respectively for males and females) in the 400 ppm group. The nasal cavity, lung, liver, and kidney were identified as potential target sites for divinylbenzene-HP based upon nasal lesions and increases in organ weights, primarily in the 200 and 400 ppm groups. Repeated inhalation exposure of rats to 200 or 400 ppm divinylbenzene-HP produced a minimal or mild rhinitis in both sexes. Microscopic lesions attributed to divinylbenzene-HP exposure were not observed in the lung, liver, or kidney of rats.

Mice were more susceptible than rats to divinylbenzene-HP toxicity. Two of five mice of both sexes exposed to 200 ppm, and all mice exposed to 400 ppm died during the 2-week study. As was observed in the rat, the nasal cavity, liver, and kidney were identified as potential target sites for divinylbenzene-HP. Liver and kidney weights were mildly increased in male and/or female mice in all exposed groups; however, these increases were not exposure concentration related. Lesions associated with exposure of mice to divinylbenzene-HP varied with exposure concentration and length of survival. Mice exposed to 400 ppm all died early with periportal hepatic degeneration and necrosis of respiratory, transitional, and olfactory epithelium and nasal glands in all levels of the nasal cavity. Mice exposed to 200 ppm had centrilobular hepatic karyomegaly similar to lesions reported for styrene-exposed mice (Morgan *et al*., 1993; Mahler *et al*., 1999). A spectrum of renal lesions was seen in the 200 ppm group with tubular necrosis, mineralization, and casts prominent in mice that died early, and tubular regeneration more prominent in survivors. Nasal lesions in the 200 ppm group included those found in the 400 ppm group with the addition of some more chronic changes, squamous metaplasia, glandular hyperplasia, and olfactory atrophy and metaplasia, particularly in the surviving mice. Mice exposed to 100 ppm had minimal to mild changes in the olfactory region of the nose including Bowman's glands. Similar lesions were found in mice exposed to 25 or 50 ppm.

Because only mild effects were observed in rats exposed to 25 to 400 ppm divinylbenzene-HP for 2 weeks, the same concentrations were used in the 3-month study. There were no deaths in the 3-month rat study, and only males exposed to 400 ppm had a modest decrease in body weights (10%). Liver and kidney weights were increased in all exposed male groups and in females exposed to 400 ppm. No renal or hepatic lesions were seen in rats. Minimal to mild degeneration and basal cell hyperplasia of olfactory epithelium were present in both sexes after 3 months. The incidence and severity of basal cell hyperplasia were exposure concentration related. The vast majority of degenerative lesions were graded as minimal severity.

B6C3F$_1$ mice were found to be more susceptible than F344/N rats to divinylbenzene-HP in the 2-week study and were exposed to a lower concentration range (12.5, 25, 50, 100, or 200 ppm) for 3 months. Although 200 ppm divinylbenzene-HP caused some mortality in the 2-week study, a previous styrene study demonstrated that mice surviving the initial exposure survived continued exposure and had little evidence of liver toxicity after 3 months. However, in the current 3-month study, mice did not develop resistance to 200 ppm divinylbenzene-HP as observed for styrene. Of the mice exposed to 200 ppm divinylbenzene-HP, all but one died early with centrilobular hepatocellular necrosis and mineralization. Nearly all mice exposed to 200 ppm also had moderate to marked renal tubular necrosis, accompanied by casts and mineralization. In both sexes of mice, the mean final body weights were significantly lower for all groups exposed to 25 ppm or more compared to their respective chamber controls.

As was observed in rats, the nasal cavity was a primary target site of inhaled divinylbenzene-HP in mice. Necrosis of olfactory epithelium and associated glands was the prominent nasal lesion in moribund and dead mice exposed to 200 ppm. After 3 months, there was still evidence of olfactory necrosis in mice exposed to 25 ppm or greater. More prominent lesions in those exposed groups were olfactory atrophy and hyaline degeneration, glandular hyperplasia, a mixed inflammatory cell infiltrate, and hyaline degeneration of respiratory epithelium.

There was no evidence of reproductive toxicity in male or female rats or mice in the 3-month studies based on sperm motility and vaginal cytology evaluations.

The results of these 3-month divinylbenzene-HP studies are consistent with earlier subchronic studies of styrene that demonstrated similar toxicological properties for divinylbenzene-HP and styrene. Both chemicals were more toxic for mice than rats (Roycroft *et al*., 1992; Morgan *et al*., 1997) and both caused nasal toxicity and hepatotoxicity in mice (Roycroft *et al.,* 1992; Morgan *et al*., 1993; 1997). Morgan *et al.* (1997) reported that divinylbenzene-55, a less pure form of divinylbenzene than that used in the current study, was more acutely toxic than a similar concentration of styrene. Similarly, in the current 3-month mouse study, 200 ppm divinylbenzene-HP caused significantly greater mortality than exposure to 250 ppm styrene for 3 months. The species difference in susceptibility to styrene has been attributed to greater epoxidase activity and less epoxide hydrolase activity in mice relative to rats (Glatt and Oesch, 1987). A similar mechanism is likely for this species difference in susceptibility to divinylbenzene-HP.

The modest effect on body weight and the slight severity of lesions induced in rats by exposure to divinylbenzene-HP for 3 months indicated that these same concentrations could be used in a chronic study in rats without causing mortality due to toxicity. In the current 2-year study, male and female rats were exposed to 0, 100, 200, or 400 ppm divinylbenzene-HP. Survival rates were comparable between chamber control and exposed rats (61%-70%), except the 400 ppm females in which the survival (44%) was significantly reduced. Mean body weights among surviving 400 ppm males and females were significantly lower than the chamber controls at terminal sacrifice.

As observed in the 3-month mouse study, the kidney also was a target site for divinylbenzene-HP in the 2-year rat study. Marginal increases in renal tubule carcinoma were diagnosed in male rats exposed to 400 ppm. Although not statistically significant relative to concurrent chamber controls, the incidence of renal tubule carcinoma exceeded the historical control incidence. A statistically significant increase in the incidence of chronic nephropathy and increased severity of renal tubule hyperplasia were also present in male rats exposed to 400 ppm divinylbenzene-HP. In the kidney, renal tubule hyperplasia, adenoma, and carcinoma are thought to represent a continuum in the progression of proliferative lesions. Because of the marginally increased incidence of carcinoma and the advanced renal tubule hyperplasia in the 400 ppm group, an extended evaluation (step sectioning) of the kidney was performed in the males. In the extended evaluation, renal tubule adenomas were identified in two 200 ppm and one 400 ppm males; no additional renal tubule carcinomas were identified. However, the incidences of adenoma, carcinoma, and adenoma or carcinoma (combined) in the exposed groups were not statistically significant relative to concurrent or historical controls for 2-year inhalation studies. Based upon these results, a clear relationship between kidney neoplasms and divinylbenzene-HP exposure could not be determined.

The incidences of basal cell adenoma of the skin were slightly increased in male rats exposed to 200 or 400 ppm divinylbenzene-HP. Basal cell adenomas were composed predominantly of basal cells or a mixture of sebaceous and keratinizing squamous epithelium, often forming cysts. The basal cell adenomas were not accompanied by any carcinomas, and their slightly increased incidences were within the range for historical controls by all routes of administration; thus they were not considered related to exposure to divinylbenzene-HP.

The brain was a potential target site for divinylbenzene-HP in rats. Incidences of malignant astrocytoma in 200 ppm males and females and malignant oligodendroglioma in 100 and 200 ppm males were not significantly greater than those in the concurrent chamber controls but exceeded the historical ranges in chamber control rats. The incidences of malignant astrocytoma or malignant oligodendroglioma (combined) were slightly increased in 100 and 200 ppm males, and the incidence in the 200 ppm group exceeded the historical incidence for chamber controls. Although the incidence of these malignant glial cell neoplasms did not increase with increasing exposure concentration, an association with exposure to divinylbenzene-HP could not be excluded, and these neoplasms were therefore considered an equivocal finding.

As observed in 3-month study, the nasal cavity was a major target site for divinylbenzene-HP in the 2-year study in rats. Inhalation exposure to divinylbenzene-HP for up to 105 weeks induced nonneoplastic lesions including degeneration and basal cell hyperplasia of the nasal olfactory epithelium and dilatation of adjacent Bowman's glands. These lesions were mostly minimal to mild in severity and reflect the cytotoxic and regenerative responses reported in the 3-month study and in short-term inhalation studies of divinylbenzene-55 by Morgan *et al.* (1997). Similar nasal lesions were reported in rats after a 2-year inhalation exposure to styrene (Cruzan *et al.,* 1998). Olfactory lesions were observed after exposure to 50 ppm styrene or greater. The incidence and severity of epithelial degeneration in the current study were comparable between sexes and among all divinylbenzene-HP exposure concentrations, while the incidences (both sexes) of basal cell hyperplasia and glandular dilatation were lower at the 100 ppm level relative to the higher exposure concentrations. There was also an exposure concentration related increase in goblet cell hyperplasia among males. This response has been attributed to the direct irritant properties to divinylbenzene-HP (Alarie, 1981; De Ceaurriz *et al*., 1981; Alarie *et al*., 1995).

Based on the results of the 3-month studies, mice were exposed to divinylbenzene-HP concentrations of 0, 10, 30, or 100 ppm for 2 years. Survival of all exposed groups of mice was similar to that of the chamber controls. The lung was a target organ of divinylbenzene-HP exposure in mice but not in rats. In the lungs of male mice exposed to 100 ppm divinylbenzene-HP, the incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) were marginally greater than those in concurrent controls and were at or above the upper end of the historical ranges for chamber controls. In exposed female mice, the incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) were generally increased and exceeded the historical control ranges, although the increases were not statistically significant and did not increase with increasing exposure concentration. Lung tumors were also reported in a 2-year inhalation exposure of CD-1 mice to styrene (20, 40, 80, or 160 ppm) (Cruzan *et al*., 2001). Styrene inhalation caused an increased incidence of pulmonary adenomas in male and female mice and an increase in alveolar/bronchiolar carcinomas in female mice exposed to 160 ppm. As in the current study of divinylbenzene-HP, the lung was not a target for styrene in the rat. In the current study, divinylbenzene-HP also caused a number of nonneoplastic lesions in the mouse lung. Atypical bronchiolar hyperplasia was present in all exposed male and female mice. The incidences and severity of this lesion increased with increasing exposure concentration. The atypical bronchiolar hyperplasia was characterized by enlarged karyomegalic cells that were piled up and occasionally formed intralumenal papillary projections.

Alveolar epithelial hyperplasia was increased in all exposed groups of males and reached statistical significance in the 100 ppm group. The incidence of alveolar epithelial hyperplasia was marginally increased in 100 ppm females, and the severity of the lesion increased in the 30 and 100 ppm groups. A progression of nonneoplastic effects was observed in the lungs of CD-1 mice exposed to styrene for 2 years (Cruzan *et al*., 2001). Lung lesions progressed from decreased eosinophilia of the epithelium of the terminal bronchioles (52 weeks) to hyperplasia of the terminal bronchiolar epithelium (78 weeks) and finally to hyperplasia extending into the alveolar ducts (104 weeks).
A single incidence of olfactory epithelium neuroblastoma occurred in 100 ppm female mice. Although this lesion was marginal and did not involve bone, this lesion has not been observed in historical chamber control female mice. Incidences of nonneoplastic nasal lesions were significantly increased in exposed mice and were similar to those observed in exposed rats. Suppurative inflammation and metaplasia of the respiratory epithelium of Bowman's glands and olfactory epithelium were present in all exposed mice, and the severity of these lesions

increased with increasing divinylbenzene-HP exposure concentration. Styrene inhalation has been shown to cause similar nonneoplastic lesions in the nasal cavity of rats and mice (Roycroft *et al*., 1992; Morgan *et al*., 1993; Cruzan *et al*., 2001). Pretreatment of mice with an inhibitor of P450 CYP2E1 and CYP2F completely prevented the nasal lesions caused by styrene. These data indicate that a metabolite of styrene (e.g., styrene oxide) and not styrene was responsible for nasal toxicity (Green *et al*., 2001b). A similar mechanism may explain the nasal toxicity of divinylbenzene-HP.

CONCLUSIONS

Under the conditions of this 2-year inhalation study, there was *equivocal evidence of carcinogenic activity** of divinylbenzene-HP in male F344/N rats based upon the occurrence of carcinomas in the kidney and glial tumors in the brain. There was *no evidence of carcinogenic activity* in female F344/N rats exposed to 100, 200, or 400 ppm divinylbenzene-HP. There was *no evidence of carcinogenic activity* in male B6C3F$_1$ mice exposed to 10, 30, or 100 ppm divinylbenzene-HP. There was *equivocal evidence of carcinogenic activity* of divinylbenzene-HP in female B6C3F$_1$ mice based on the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in the lung.

Exposure to divinylbenzene-HP caused nonneoplastic lesions in the nasal cavity of male and female rats including degeneration of the olfactory epithelium and basal cell epithelial hyperplasia. Nonneoplastic lesions were observed in the lung and nasal cavity of exposed mice. Atypical bronchiolar hyperplasia and hyperplasia of the alveolar epithelium were observed in lung of male and female mice. In the nasal cavity of mice, suppurative inflammation, metaplasia of the respiratory and olfactory epithelium, and degeneration of the olfactory epithelium were present at all concentrations.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 12.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF DIVINYLBENZENE-HP

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Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	15	9	12	13
Natural deaths	4	6	6	5
Survivors				
Died last week of the study			1	
Terminal sacrifice	31	35	31	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, rectum	(48)	(48)	(48)	(49)
Adenoma		1 (2%)		
Polyp adenomatous			1 (2%)	
Intestine large, cecum	(47)	(48)	(46)	(49)
Polyp adenomatous		1 (2%)		
Intestine small, jejunum	(46)	(47)	(47)	(46)
Histiocytic sarcoma, metastatic, mesentery	1 (2%)			
Intestine small, ileum	(46)	(47)	(45)	(46)
Fibrosarcoma				1 (2%)
Liver	(50)	(49)	(50)	(50)
Carcinoma, metastatic, islets, pancreatic				1 (2%)
Fibrous histiocytoma, metastatic, skin		1 (2%)		1 (2%)
Osteosarcoma, metastatic, bone	1 (2%)			
Osteosarcoma, metastatic, uncertain primary site		1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)	
Mesentery	(12)	(13)	(18)	(11)
Carcinoma, metastatic, kidney				1 (9%)
Histiocytic sarcoma	1 (8%)			
Leiomyosarcoma, metastatic, stomach, glandular	1 (8%)			
Oral mucosa	(1)		(1)	(4)
Pharyngeal, squamous cell papilloma				1 (25%)
Pancreas	(50)	(49)	(50)	(50)
Carcinoma, metastatic, kidney				1 (2%)
Fibrous histiocytoma, metastatic, skin		1 (2%)		
Histiocytic sarcoma, metastatic, mesentery	1 (2%)			
Leiomyosarcoma, metastatic, stomach, glandular	1 (2%)			
Acinus, adenoma				1 (2%)
Stomach, forestomach	(50)	(48)	(50)	(50)
Histiocytic sarcoma, metastatic, mesentery	1 (2%)			
Stomach, glandular	(50)	(48)	(50)	(49)
Leiomyosarcoma	1 (2%)			
Tongue	(1)	(1)		
Squamous cell papilloma	1 (100%)			
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Heart	(50)	(50)	(50)	(50)

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney				1 (2%)
Osteosarcoma, metastatic, bone		1 (2%)		
Adrenal medulla	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, bone	1 (2%)			
Pheochromocytoma malignant	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Pheochromocytoma benign	12 (24%)	3 (6%)	8 (16%)	7 (14%)
Bilateral, pheochromocytoma benign		1 (2%)	1 (2%)	
Islets, pancreatic	(50)	(48)	(50)	(50)
Adenoma	5 (10%)	8 (17%)	2 (4%)	9 (18%)
Carcinoma	1 (2%)		1 (2%)	1 (2%)
Pituitary gland	(50)	(50)	(50)	(49)
Pars distalis, adenoma	36 (72%)	30 (60%)	31 (62%)	29 (59%)
Pars distalis, ganglioneuroma				1 (2%)
Pars intermedia, adenoma		2 (4%)		
Thyroid gland	(50)	(50)	(50)	(49)
C-cell, adenoma	2 (4%)	5 (10%)	2 (4%)	2 (4%)
C-cell, carcinoma	1 (2%)			1 (2%)
Follicular cell, adenoma	1 (2%)			
General Body System				
Peritoneum	(40)	(49)	(50)	(49)
Carcinoma, metastatic, kidney				1 (2%)
Histiocytic sarcoma, metastatic, mesentery	1 (3%)			
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(48)	(50)	(50)	(49)
Adenoma		1 (2%)		1 (2%)
Carcinoma		1 (2%)		1 (2%)
Prostate	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney				1 (2%)
Histiocytic sarcoma, metastatic, mesentery	1 (2%)			
Seminal vesicle	(50)	(49)	(50)	(50)
Carcinoma, metastatic, kidney				1 (2%)
Histiocytic sarcoma, metastatic, mesentery	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	20 (40%)	32 (64%)	27 (54%)	32 (64%)
Interstitial cell, adenoma	18 (36%)	13 (26%)	16 (32%)	10 (20%)

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin		1 (2%)		
Lymph node	(11)	(5)	(11)	(6)
Lymph node, bronchial	(7)	(6)	(12)	(5)
Lymph node, mesenteric	(49)	(49)	(50)	(50)
Carcinoma, metastatic, kidney				1 (2%)
Sarcoma	1 (2%)			
Lymph node, mediastinal	(19)	(23)	(25)	(38)
Carcinoma, metastatic, kidney				1 (3%)
Spleen	(50)	(49)	(50)	(50)
Carcinoma, metastatic, kidney				1 (2%)
Fibrous histiocytoma, metastatic, skin		1 (2%)		1 (2%)
Histiocytic sarcoma, metastatic, mesentery	1 (2%)			
Thymus	(48)	(44)	(46)	(42)
Integumentary System				
Mammary gland	(35)	(43)	(47)	(48)
Adenoma, multiple		1 (2%)		
Carcinoma	1 (3%)		1 (2%)	
Fibroadenoma	1 (3%)		5 (11%)	1 (2%)
Fibroadenoma, multiple				1 (2%)
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma			1 (2%)	3 (6%)
Squamous cell papilloma	1 (2%)			
Trichoepithelioma	1 (2%)			
Subcutaneous tissue, fibroma	5 (10%)	7 (14%)	4 (8%)	3 (6%)
Subcutaneous tissue, fibrous histiocytoma		1 (2%)		1 (2%)
Subcutaneous tissue, fibrous histiocytoma, multiple	1 (2%)			
Subcutaneous tissue, lipoma	1 (2%)	1 (2%)	1 (2%)	
Subcutaneous tissue, myxoma				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Femur, osteosarcoma		1 (2%)		
Pelvis, femur, osteosarcoma	1 (2%)			
Skeletal muscle	(2)	(6)	(1)	(4)
Carcinoma, metastatic, kidney				1 (25%)
Fibrous histiocytoma, metastatic, skin		1 (17%)		
Osteosarcoma		1 (17%)		
Nervous System				
Brain	(49)	(50)	(50)	(50)
Astrocytoma malignant			2 (4%)	
Oligodendroglioma malignant		1 (2%)	1 (2%)	

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)		
Alveolar/bronchiolar adenoma, multiple				1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)		1 (2%)	
Carcinoma, metastatic, kidney				1 (2%)
Fibrous histiocytoma, metastatic, skin	1 (2%)	1 (2%)		1 (2%)
Histiocytic sarcoma, metastatic, mesentery	1 (2%)			
Osteosarcoma, metastatic, bone	1 (2%)	1 (2%)		
Osteosarcoma, metastatic, uncertain primary site		1 (2%)		
Squamous cell carcinoma			1 (2%)	
Nose	(50)	(48)	(50)	(49)
Pleura	(50)	(50)	(50)	(50)
Histiocytic sarcoma, metastatic, mesentery	1 (2%)			
Leiomyosarcoma, metastatic, stomach, glandular	1 (2%)			
Special Senses System				
Zymbal's gland	(1)		(3)	
Carcinoma			2 (67%)	
Urinary System				
Kidney	(50)	(49)	(50)	(49)
Histiocytic sarcoma, metastatic, mesentery	1 (2%)			
Liposarcoma	1 (2%)			
Pelvis, transitional epithelium, carcinoma	1 (2%)	1 (2%)		
Renal tubule, carcinoma				2 (4%)
Urinary bladder	(50)	(49)	(50)	(49)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Leukemia mononuclear	22 (44%)	13 (26%)	14 (28%)	10 (20%)
Mesothelioma malignant	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	50	49	49	49
Total primary neoplasms	140	130	125	123
Total animals with benign neoplasms	49	49	48	48
Total benign neoplasms	104	107	99	103
Total animals with malignant neoplasms	29	20	24	18
Total malignant neoplasms	36	23	26	20
Total animals with metastatic neoplasms	5	3	1	3
Total metastatic neoplasms	19	10	1	15
Total animals with malignant neoplasms of uncertain primary site		1		

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	355	506	536	543	561	589	589	612	612	623	638	666	670	675	682	701	704	722	725	729	729	729	729	729	729
Carcass ID Number	009	002	017	018	041	001	015	035	044	023	031	039	016	027	034	050	006	019	028	008	010	011	012	013	014
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, mesentery																									
Intestine small, ileum	+	+	+	+	A	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone			X																						
Mesentery														+	+		+	+		+			+		
Histiocytic sarcoma																									
Leiomyosarcoma, metastatic, stomach, glandular														X											
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, mesentery																									
Leiomyosarcoma, metastatic, stomach, glandular														X											
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, mesentery																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma														X											
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, peritoneum																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	020	021	022	024	025	026	029	033	038	043	046	048	003	004	037	040	045	047	005	007	030	032	036	042	049	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma, metastatic, mesentery										X																1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Mesentery	+					+				+	+		+			+										12
Histiocytic sarcoma										X																1
Leiomyosarcoma, metastatic, stomach, glandular																										1
Oral mucosa														+												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, mesentery										X																1
Leiomyosarcoma, metastatic, stomach, glandular																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, mesentery										X																1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Tongue								+																		1
Squamous cell papilloma								X																		1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, peritoneum											X															1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	3	5	5	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	5	0	3	4	6	8	8	1	1	2	3	6	7	7	8	0	0	2	2	2	2	2	2	2	2
	5	6	6	3	1	9	9	2	2	3	8	6	0	5	2	1	4	5	5	9	9	9	9	9	9
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	1	1	4	0	1	3	4	2	3	3	1	2	3	5	0	1	2	0	1	1	1	1	1
	9	2	7	8	1	1	5	5	4	3	1	9	6	7	4	0	6	9	8	8	0	1	2	3	4
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone			X																						
Pheochromocytoma malignant																									
Pheochromocytoma benign										X	X	X							X					X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X															X						
Carcinoma																									
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X		X				X	X		X	X	X	X	X	X		X	X	X	X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, adenoma						X																			
General Body System																									
Peritoneum	+	+	+	+	+	+	+	+	+		+	+			+	+	+		+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, mesentery																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, mesentery																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, mesentery																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma								X	X											X	X	X	X	X	
Interstitial cell, adenoma				X	X		X			X			X					X							X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+						+	+	+				+		+		+	+							
Lymph node, bronchial	M	M	M	+	+	M	M	M	M	M	M	+	+	+	M	M	M	+	M	M	M	M	M	M	M
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Lymph node, mediastinal	M	+	M	M	+	M	M	M	+	M	+	M	+	M	+	M	+	+	M	M	M	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, mesentery																									
Thymus	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	020	021	022	024	025	026	029	033	038	043	046	048	003	004	037	040	045	047	005	007	030	032	036	042	049	Total Tissues/ Tumors
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Pheochromocytoma malignant	X																									1
Pheochromocytoma benign							X			X			X							X	X			X	X	12
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																			X			X		X		5
Carcinoma															X											1
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X	X	X	X	X	X	X	X	X	X			X	X		X			X	X	X	X	36
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X																					X			2
C-cell, carcinoma										X																1
Follicular cell, adenoma																										1
General Body System																										
Peritoneum		+				+	+	+		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	40
Histiocytic sarcoma, metastatic, mesentery										X																1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, mesentery										X																1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, mesentery										X																1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X		X		X	X			X	X	X				X		X		X	X			X	X	20
Interstitial cell, adenoma	X		X		X			X					X	X	X		X		X			X	X			18
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node								+			+												+			11
Lymph node, bronchial	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	7
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma			X																							1
Lymph node, mediastinal	M	+	M	M	M	M	M	M	+	M	+	M	M	M	M	M	M	+	+	M	M	+	+	M	+	19
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, mesentery										X																1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	355	506	536	543	561	589	589	612	612	623	638	666	670	675	682	701	704	725	725	729	729	729	729	729	729
Carcass ID Number	009	002	017	018	041	001	015	035	044	023	031	039	016	027	034	050	006	019	028	008	010	011	012	013	014
Integumentary System																									
Mammary gland	+	+	M	+	+	+	M	+	+	+	M	+	+	+	M	M	+	+	+	+	M	M	M	+	M
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma										X															
Trichoepithelioma																									
Subcutaneous tissue, fibroma			X							X												X		X	
Subcutaneous tissue, fibrous histiocytoma, multiple																		X							
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, femur, osteosarcoma			X																						
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Larynx	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Fibrous histiocytoma, metastatic, skin																		X							
Histiocytic sarcoma, metastatic, mesentery																									
Mesothelioma malignant, metastatic, peritoneum																									
Osteosarcoma, metastatic, bone			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, mesentery																									
Leiomyosarcoma, metastatic, stomach, glandular														X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																									

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	020	021	022	024	025	026	029	033	038	043	046	048	003	004	037	040	045	047	005	007	030	032	036	042	049	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	M	+	35
Carcinoma											X															1
Fibroadenoma											X															1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Trichoepithelioma														X												1
Subcutaneous tissue, fibroma															X											5
Subcutaneous tissue, fibrous histiocytoma, multiple																										1
Subcutaneous tissue, lipoma												X														1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pelvis, femur, osteosarcoma																										1
Skeletal muscle											+			+												2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Peripheral nerve														+												1
Spinal cord														+												1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma													X													1
Fibrous histiocytoma, metastatic, skin																										1
Histiocytic sarcoma, metastatic, mesentery										X																1
Mesothelioma malignant, metastatic, peritoneum											X															1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, mesentery										X																1
Leiomyosarcoma, metastatic, stomach, glandular																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Zymbal's gland																	+									1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	355	506	536	543	561	589	589	612	612	623	638	666	670	675	682	701	704	725	725	729	729	729	729	729	729
Carcass ID Number	009	002	017	018	041	001	015	035	044	023	031	039	016	027	034	050	006	019	028	008	010	011	012	013	014
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, mesentery																									
Liposarcoma																									
Pelvis, transitional epithelium, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear	X			X	X		X	X	X			X	X	X	X		X	X	X				X	X	
Mesothelioma malignant														X											

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	020	021	022	024	025	026	029	033	038	043	046	048	003	004	037	040	045	047	005	007	030	032	036	042	049	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, mesentery										X																1
Liposarcoma		X																								1
Pelvis, transitional epithelium, carcinoma		X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma										X																1
Leukemia mononuclear	X						X	X	X							X			X						X	22
Mesothelioma malignant											X															2

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	106	393	569	582	605	654	654	659	682	704	708	710	717	722	728	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	244	234	205	202	210	220	250	239	215	232	216	233	231	207	221	203	206	208	217	223	224	235	236	237	240
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Intestine large, cecum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, duodenum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin												X													
Osteosarcoma, metastatic, uncertain primary site																									
Mesentery		+						+					+			+					+		+	+	
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin												X													
Salivary glands	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue									+																
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone					X																				
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Adenoma										X							X								
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X		X	X	X	X	X				X	X					X			X		X	X
Pars intermedia, adenoma																							X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X																	X	X	X

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	9	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	Total
	4	4	0	1	1	1	2	2	2	2	2	3	3	4	4	0	0	1	1	1	2	4	4	4	4	Tissues/
	7	8	4	2	4	8	2	5	6	7	8	0	8	1	3	1	9	1	3	9	9	2	5	6	9	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous												X														1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, skin																										1
Osteosarcoma, metastatic, uncertain primary site																		X								1
Mesentery			+		+		+					+	+								+					13
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, skin																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant											X					X										2
Pheochromocytoma benign				X								X	X													3
Bilateral, pheochromocytoma benign																			X							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma				X	X				X								X					X	X			8
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X			X	X	X	X	X		X		X	X	X	X		X	X		X		30
Pars intermedia, adenoma													X													2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma				X																						5

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	106	393	569	582	605	654	654	659	682	704	708	710	717	722	728	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	244	234	205	202	210	220	250	239	215	232	216	233	231	207	221	203	206	208	217	223	224	235	236	237	240
General Body System																									
Peritoneum		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Genital System																									
Coagulating gland		+																							
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Carcinoma		X																							
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma								X	X	X	X	X		X	X	X	X	X	X	X	X	X			X
Interstitial cell, adenoma		X	X	X		X							X										X	X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin												X													
Lymph node			+		+						+													+	
Lymph node, bronchial	M	M	M	M	M	M	M	M	M	M	+	M	+	M	M	M	M	M	M	M	M	M	M	+	M
Lymph node, mandibular	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	A	M	+	M	+	M	M	M	+	+	+	+	+	+	+	+	M	M	M	M	+	M	M	M	M
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin												X													
Thymus	+	M	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	M	+	+
Adenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma								X																	X
Subcutaneous tissue, fibrous histiocytoma												X													
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma					X																				
Skeletal muscle								+				+										+			
Fibrous histiocytoma, metastatic, skin												X													
Osteosarcoma																						X			

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	9	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	Total
Carcass ID Number	4	4	0	1	1	1	2	2	2	2	2	3	3	4	4	0	0	1	1	1	2	4	4	4	4	Tissues/
	7	8	4	2	4	8	2	5	6	7	8	0	8	1	3	1	9	1	3	9	9	2	5	6	9	Tumors
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma				X	X	X	X	X				X		X	X	X		X	X	X	X	X	X	X	X	32
Interstitial cell, adenoma	X		X						X	X	X		X													13
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Lymph node																+										5
Lymph node, bronchial	M	+	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	6
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	M	+	M	M	M	M	+	+	+	M	M	M	M	+	+	+	M	M	+	M	+	+	+	M	+	23
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, skin																										1
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	43
Adenoma, multiple									X																	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma									X		X	X				X								X		7
Subcutaneous tissue, fibrous histiocytoma																										1
Subcutaneous tissue, lipoma													X													1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femur, osteosarcoma																										1
Skeletal muscle													+						+				+			6
Fibrous histiocytoma, metastatic, skin																										1
Osteosarcoma																										1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	106	393	569	582	605	654	654	659	682	704	708	710	717	722	728	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	244	234	205	202	210	220	250	239	215	232	216	233	231	207	221	203	206	208	217	223	224	235	236	237	240
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma malignant				X																					
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Larynx	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Fibrous histiocytoma, metastatic, skin												X													
Osteosarcoma, metastatic, bone					X																				
Osteosarcoma, metastatic, uncertain primary site																									
Nose	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, transitional epithelium, carcinoma																									
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X				X	X	X			X	X					X		X			
Mesothelioma malignant																									

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	247	248	204	212	214	218	222	225	226	227	228	230	238	241	243	201	209	211	213	219	229	242	245	246	249	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma malignant																										1
Peripheral nerve													+						+							2
Spinal cord													+						+				+			3
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X															1
Fibrous histiocytoma, metastatic, skin																										1
Osteosarcoma, metastatic, bone																										1
Osteosarcoma, metastatic, uncertain primary site																		X								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pelvis, transitional epithelium, carcinoma																					X					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X							X		X							X	13
Mesothelioma malignant															X					X						2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 200 ppm

Number of Days on Study	1	4	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
	1	6	4	6	7	8	1	1	5	6	7	8	9	9	1	2	2	2	2	2	2	2	2	2	2
	4	0	4	8	8	6	7	9	3	1	6	7	4	4	7	2	2	3	9	9	9	9	9	9	9
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	2	2	4	0	3	2	1	3	1	0	3	0	0	1	2	2	3	4	0	1	1	1	2	2	2
	0	1	9	9	8	4	8	9	4	5	4	7	8	7	7	5	0	5	6	0	1	5	2	3	9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine large, cecum	A	A	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, metastatic, adrenal medulla																	X								
Mesentery			+		+			+		+		+		+				+		+	+				+
Oral mucosa											+														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																	X								
Pheochromocytoma benign																X						X			
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Carcinoma																								X	
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X	X	X	X	X	X	X	X		X	X	X		X	X	X		X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																				X					
General Body System																									
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 200 ppm

Number of Days on Study	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	
Carcass ID Number	433	436	437	442	443	444	401	404	419	426	428	431	432	440	441	447	402	403	412	413	416	435	446	448	450	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous							X																			1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Mesentery		+	+	+							+		+				+							+	+	18
Oral mucosa																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant											X															2
Pheochromocytoma benign				X				X	X						X		X								X	8
Bilateral, pheochromocytoma benign													X													1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											2
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X	X	X		X	X		X	X			X	X		X		X		X	X		X	31
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																			X							2
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 200 ppm

Number of Days on Study	114	460	544	568	578	586	617	619	653	661	676	687	694	694	717	722	722	723	729	729	729	729	729	729	729
Carcass ID Number	420	421	449	409	438	424	418	439	414	405	434	407	408	417	427	425	430	445	406	410	411	415	422	423	429
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																+				+					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X	X	X					X						X			X		X	X		X	X
Interstitial cell, adenoma		X				X	X				X	X		X	X		X								
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+	+							+				+			+					+		+
Lymph node, bronchial	M	+	M	+	M	M	M	M	M	M	M	M	M	M	+	+	+	M	M	M	M	M	M	M	M
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	+	M	+	M	M	M	+	M	M	+	M	+	+	M	M	+	+	M	+	+	M	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma					X																				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma					X																				
Subcutaneous tissue, fibroma																						X			
Subcutaneous tissue, lipoma																									X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																			X						
Oligodendroglioma malignant																									
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Squamous cell carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 200 ppm

Number of Days on Study	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	
Carcass ID Number	433	436	437	442	443	444	401	404	419	426	428	431	432	440	441	447	402	403	412	413	416	435	446	448	450	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X			X			X	X	X	X	X	X		X			X	X	X	27
Interstitial cell, adenoma			X					X	X		X	X							X		X	X				16
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+																	+				+		11
Lymph node, bronchial	+	M	M	M	M	M	M	M	M	+	+	+	M	M	M	+	+	M	M	M	M	M	M	+	M	12
Lymph node, mandibular	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	+	+	M	4
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	M	M	M	M	+	+	+	+	+	M	M	M	+	M	M	+	+	+	+	M	+	M	+	+	M	25
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Carcinoma																									X	1
Fibroadenoma						X					X									X					X	5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Subcutaneous tissue, fibroma											X						X			X						4
Subcutaneous tissue, lipoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																		+								1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																				X						2
Oligodendroglioma malignant										X																1
Peripheral nerve																		+								1
Spinal cord																		+								1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																								X		1
Squamous cell carcinoma									X																	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 200 ppm

Number of Days on Study	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	
Carcass ID Number	433	436	437	442	443	444	401	404	419	426	428	431	432	440	441	447	402	403	412	413	416	435	446	448	450	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Zymbal's gland															+							+				3
Carcinoma																						X				2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X	X						X		X		X			X				X		14
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 200 ppm

Number of Days on Study	114	460	544	568	578	586	617	619	653	661	676	687	694	694	717	722	722	723	729	729	729	729	729	729	729
Carcass ID Number	420	421	449	409	438	424	418	439	414	405	434	407	408	417	427	425	430	445	406	410	411	415	422	423	429
Special Senses System																									
Eye	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland														+											
Carcinoma														X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra					+																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X											X	X		X				X			X
Mesothelioma malignant											X														

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 400 ppm

Number of Days on Study	513	562	567	569	589	614	633	638	674	680	680	682	687	694	708	710	723	724	729	729	729	729	729	729	729
Carcass ID Number	614	609	602	645	643	630	634	612	629	633	647	628	613	637	621	650	640	617	603	605	606	608	616	618	620
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Fibrosarcoma										X															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic																									
Fibrous histiocytoma, metastatic, skin																	X								
Mesentery							+		+	+	+	+													
Carcinoma, metastatic, kidney												X													
Oral mucosa			+							+															
Pharyngeal, squamous cell papilloma										X															
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney												X													
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney												X													
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant											X														
Pheochromocytoma benign									X												X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X	X						X								X				
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X	X	X	X	X	X		X		X	X		X					X		
Pars distalis, ganglioneuroma																			X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
General Body System																									
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney												X													

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 400 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	731	731	731	731	731	731	731	731	
Carcass ID Number	625	626	627	632	636	639	641	644	646	648	649	601	607	619	631	635	642	604	610	611	615	622	623	624	638	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibrosarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic												X														1
Fibrous histiocytoma, metastatic, skin																										1
Mesentery				+						+		+				+		+			+					11
Carcinoma, metastatic, kidney																										1
Oral mucosa		+			+																					4
Pharyngeal, squamous cell papilloma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Acinus, adenoma											X															1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign								X				X										X	X	X		7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X	X			X					X			X					9
Carcinoma												X														1
Parathyroid gland	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X		X	X	X	X		X	X		X	X	X	X	X		X	X	X		X	X	X		29
Pars distalis, ganglioneuroma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma																							X	X		2
C-cell, carcinoma														X												1
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney																										1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 400 ppm

Number of Days on Study	513	562	567	569	589	614	633	638	674	680	680	682	687	694	708	710	723	724	729	729	729	729	729	729	729
Carcass ID Number	614	609	602	645	643	630	634	612	629	633	647	628	613	637	621	650	640	617	603	605	606	608	616	618	620
Genital System																									
Coagulating gland											+														
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Carcinoma								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney												X													
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney												X													
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X	X	X				X	X	X			X	X	X	X		X	X	X	X	X		X
Interstitial cell, adenoma		X				X		X										X						X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+	+													+							
Lymph node, bronchial	M	+	M	M	M	M	M	M	M	+	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney												X													
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney												X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney												X													
Fibrous histiocytoma, metastatic, skin																	X								
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																							X		
Fibroadenoma, multiple																				X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Subcutaneous tissue, fibroma				X						X															
Subcutaneous tissue, fibrous histiocytoma																	X								
Subcutaneous tissue, myxoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle												+													
Carcinoma, metastatic, kidney												X													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 400 ppm

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	6 2 5	6 2 6	6 2 7	6 3 2	6 3 6	6 3 9	6 4 1	6 4 4	6 4 6	6 4 8	6 4 9	6 0 1	6 0 7	6 1 9	6 3 1	6 3 5	6 4 2	6 0 4	6 1 0	6 1 1	6 1 5	6 2 2	6 2 3	6 2 4	6 3 8	Total Tissues/ Tumors
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X		X			X	X	X		X	X			X			X	X	X	X	X		X	X	X	32
Interstitial cell, adenoma		X			X								X			X						X				10
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+											+									+			6
Lymph node, bronchial	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	+	M	M	5
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Lymph node, mediastinal	+	+	+	+	+	+	M	+	M	M	M	M	+	M	M	+	M	M	+	+	+	+	+	+	M	38
Carcinoma, metastatic, kidney																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Fibrous histiocytoma, metastatic, skin																										1
Thymus	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	42
Integumentary System																										
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Fibroadenoma																										1
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma	X				X							X														3
Subcutaneous tissue, fibroma																						X				3
Subcutaneous tissue, fibrous histiocytoma																										1
Subcutaneous tissue, myxoma							X																			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle					+																	+			+	4
Carcinoma, metastatic, kidney																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve					+																	+				2
Spinal cord					+																	+				2

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 400 ppm

Number of Days on Study	5 1 3	5 6 2	5 6 7	5 6 9	5 8 9	6 1 4	6 3 3	6 3 8	6 7 4	6 8 0	6 8 0	6 8 2	6 8 7	6 9 4	7 0 8	7 1 0	7 2 3	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	6 1 4	6 0 9	6 0 2	6 4 5	6 4 3	6 3 0	6 3 4	6 1 2	6 2 9	6 3 3	6 4 7	6 2 8	6 1 3	6 3 7	6 2 1	6 5 0	6 4 0	6 1 7	6 0 3	6 0 5	6 0 6	6 0 8	6 1 6	6 1 8	6 2 0
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma, multiple																									
Carcinoma, metastatic, kidney												X													
Fibrous histiocytoma, metastatic, skin																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Renal tubule, carcinoma												X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X		X							X		X		X							
Mesothelioma malignant		X																							

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 400 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	731	731	731	731	731	731	731	731	
Carcass ID Number	625	626	627	632	636	639	641	644	646	648	649	601	607	619	631	635	642	604	610	611	615	622	623	624	638	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma, multiple																X										1
Carcinoma, metastatic, kidney																										1
Fibrous histiocytoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, carcinoma																						X				2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X						X							X										X		10
Mesothelioma malignant														X												2

Table A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	12/50 (24%)	4/50 (8%)	9/50 (18%)	7/50 (14%)
Adjusted rate[b]	27.2%	8.8%	20.4%	15.5%
Terminal rate[c]	8/31 (26%)	4/35 (11%)	8/32 (25%)	6/32 (19%)
First incidence (days)	623	729 (T)	722	674
Poly-3 test[d]	P=0.248N	P=0.021N	P=0.308N	P=0.136N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	13/50 (26%)	6/50 (12%)	11/50 (22%)	8/50 (16%)
Adjusted rate	29.5%	13.2%	24.9%	17.7%
Terminal rate	9/31 (29%)	6/35 (17%)	9/32 (28%)	6/32 (19%)
First incidence (days)	623	729 (T)	722	674
Poly-3 test	P=0.236N	P=0.050N	P=0.405N	P=0.140N
Brain: Astrocytoma or Oligodendroglioma				
Overall rate	0/49 (0%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	2.2%	6.8%	0.0%
Terminal rate	0/30 (0%)	0/35 (0%)	3/32 (9%)	0/32 (0%)
First incidence (days)	—[e]	582	729 (T)	—
Poly-3 test	P=0.614N	P=0.517	P=0.126	—[f]
Kidney (Single and Step Sections): Renal Tubule Adenoma or Carcinoma				
Overall rate	0/50 (0%)	0/49 (0%)	2/50 (4%)	3/49 (6%)
Adjusted rate	0.0%	0.0%	4.5%	6.8%
Terminal rate	0/31 (0%)	0/35 (0%)	1/32 (3%)	1/32 (3%)
First incidence (days)	—	—	619	682
Poly-3 test	P=0.027	—	P=0.244	P=0.123
Mammary Gland: Fibroadenoma				
Overall rate	1/50 (2%)[g]	0/50 (0%)	5/50 (10%)[g]	2/50 (4%)
Adjusted rate	2.3%	0.0%	11.2%	4.5%
Terminal rate	1/31 (3%)	0/35 (0%)	4/32 (13%)	2/32 (6%)
First incidence (days)	729 (T)	—	578	729 (T)
Poly-3 test	P=0.240	P=0.490N	P=0.108	P=0.514
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	1/50 (2%)[g]	1/50 (2%)	5/50 (10%)[g]	2/50 (4%)
Adjusted rate	2.3%	2.2%	11.2%	4.5%
Terminal rate	1/31 (3%)	1/35 (3%)	4/32 (13%)	2/32 (6%)
First incidence (days)	729 (T)	729 (T)	578	729 (T)
Poly-3 test	P=0.316	P=0.749N	P=0.108	P=0.514
Pancreatic Islets: Adenoma				
Overall rate	5/50 (10%)	8/48 (17%)	2/50 (4%)	9/50 (18%)
Adjusted rate	11.4%	18.0%	4.5%	19.6%
Terminal rate	3/31 (10%)	7/34 (21%)	1/32 (3%)	6/32 (19%)
First incidence (days)	543	704	687	614
Poly-3 test	P=0.255	P=0.285	P=0.211N	P=0.218
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	6/50 (12%)	8/48 (17%)	3/50 (6%)	10/50 (20%)
Adjusted rate	13.7%	18.0%	6.8%	21.8%
Terminal rate	4/31 (13%)	7/34 (21%)	2/32 (6%)	7/32 (22%)
First incidence (days)	543	704	687	614
Poly-3 test	P=0.233	P=0.399	P=0.236N	P=0.234

Table A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	36/50 (72%)	30/50 (60%)	31/50 (62%)	29/49 (59%)
Adjusted rate	76.6%	63.3%	66.7%	63.1%
Terminal rate	24/31 (77%)	22/35 (63%)	20/32 (63%)	19/32 (59%)
First incidence (days)	506	569	586	614
Poly-3 test	P=0.150N	P=0.113N	P=0.197N	P=0.109N
Skin: Basal Cell Adenoma				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	2.2%	6.7%
Terminal rate	0/31 (0%)	0/35 (0%)	0/32 (0%)	3/32 (9%)
First incidence (days)	—	—	578	729 (T)
Poly-3 test	P=0.020	—	P=0.507	P=0.126
Skin: Trichoepithelioma or Basal Cell Adenoma				
Overall rate	1/50 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.3%	0.0%	2.2%	6.7%
Terminal rate	1/31 (3%)	0/35 (0%)	0/32 (0%)	3/32 (9%)
First incidence (days)	729 (T)	—	578	729 (T)
Poly-3 test	P=0.097	P=0.490N	P=0.753N	P=0.320
Skin: Squamous Papilloma, Trichoepithelioma, or Basal Cell Adenoma				
Overall rate	2/50 (4%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	4.6%	0.0%	2.2%	6.7%
Terminal rate	1/31 (3%)	0/35 (0%)	0/32 (0%)	3/32 (9%)
First incidence (days)	623	—	578	729 (T)
Poly-3 test	P=0.241	P=0.228N	P=0.492N	P=0.515
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	5/50 (10%)	7/50 (14%)	4/50 (8%)	3/50 (6%)
Adjusted rate	11.3%	15.3%	9.1%	6.6%
Terminal rate	3/31 (10%)	6/35 (17%)	4/32 (13%)	1/32 (3%)
First incidence (days)	536	659	729 (T)	569
Poly-3 test	P=0.183N	P=0.403	P=0.501N	P=0.338N
Skin (Subcutaneous Tissue): Fibroma, Myxoma, or Fibrous Histiocytoma				
Overall rate	6/50 (12%)	8/50 (16%)	4/50 (8%)	5/50 (10%)
Adjusted rate	13.6%	17.5%	9.1%	11.0%
Terminal rate	3/31 (10%)	6/35 (17%)	4/32 (13%)	2/32 (6%)
First incidence (days)	536	659	729 (T)	569
Poly-3 test	P=0.297N	P=0.413	P=0.370N	P=0.476N
Testes: Adenoma				
Overall rate	38/50 (76%)	45/50 (90%)	43/50 (86%)	42/50 (84%)
Adjusted rate	82.3%	93.2%	89.3%	86.3%
Terminal rate	30/31 (97%)	33/35 (94%)	30/32 (94%)	28/32 (88%)
First incidence (days)	543	393	460	562
Poly-3 test	P=0.509	P=0.075	P=0.232	P=0.390
Thyroid Gland (C-cell): Adenoma				
Overall rate	2/50 (4%)	5/50 (10%)	2/50 (4%)	2/49 (4%)
Adjusted rate	4.6%	11.0%	4.5%	4.6%
Terminal rate	2/31 (7%)	4/35 (11%)	2/32 (6%)	2/32 (6%)
First incidence (days)	729 (T)	654	729 (T)	729 (T)
Poly-3 test	P=0.388N	P=0.239	P=0.686N	P=0.687N

Table A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	2/50 (4%)	3/49 (6%)
Adjusted rate	7.0%	11.0%	4.5%	6.8%
Terminal rate	3/31 (10%)	4/35 (11%)	2/32 (6%)	3/32 (9%)
First incidence (days)	729 (T)	654	729 (T)	729 (T)
Poly-3 test	P=0.438N	P=0.388	P=0.490N	P=0.654N
All Organs: Mononuclear Cell Leukemia				
Overall rate	22/50 (44%)	13/50 (26%)	14/50 (28%)	10/50 (20%)
Adjusted rate	46.4%	27.8%	30.9%	21.5%
Terminal rate	9/31 (29%)	6/35 (17%)	9/32 (28%)	4/32 (13%)
First incidence (days)	355	569	544	569
Poly-3 test	P=0.013N	P=0.047N	P=0.092N	P=0.008N
All Organs: Benign Neoplasms				
Overall rate	49/50 (98%)	49/50 (98%)	48/50 (96%)	48/50 (96%)
Adjusted rate	99.8%	100.0%	98.0%	97.6%
Terminal rate	31/31 (100%)	35/35 (100%)	32/32 (100%)	32/32 (100%)
First incidence (days)	506	393	460	562
Poly-3 test	P=0.198N	P=1.000	P=0.554N	P=0.477N
All Organs: Malignant Neoplasms				
Overall rate	29/50 (58%)	20/50 (40%)	24/50 (48%)	18/50 (36%)
Adjusted rate	60.4%	41.6%	52.6%	37.5%
Terminal rate	15/31 (48%)	10/35 (29%)	16/32 (50%)	6/32 (19%)
First incidence (days)	355	393	544	562
Poly-3 test	P=0.037N	P=0.048N	P=0.288N	P=0.018N
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	49/50 (98%)	49/50 (98%)	49/50 (98%)
Adjusted rate	100.0%	100.0%	100.0%	99.3%
Terminal rate	31/31 (100%)	35/35 (100%)	32/32 (100%)	32/32 (100%)
First incidence (days)	355	393	460	562
Poly-3 test	P=0.660N	P=1.000N	P=1.000N	P=0.968N

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, brain, kidney, pancreatic islets, pituitary gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.
[g] One carcinoma occurred in an animal that also had a fibroadenoma.

Table A4a
Historical Incidence of Renal Tubule Neoplasms in Control Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence: Inhalation Studies			
Decalin	1/50	0/50	1/50
Divinylbenzene	0/50	0/50	0/50
Indium phosphide	0/50	0/50	0/50
Methyl isobutyl ketone	0/50	0/50	0/50
Naphthalene	0/49	0/49	0/49
Propylene glycol mono-*t*-butyl ether	1/50	0/50	1/50
Stoddard solvent IIC	0/50	1/50	1/50
Vanadium pentoxide	1/50	0/50	1/50
Overall Historical Incidence: Inhalation Studies			
Total (%)	3/399 (0.8%)	1/399 (0.3%)	4/399 (1.0%)
Mean ± standard deviation	0.8% ± 1.0%	0.3% ± 0.7%	1.0% ± 1.1%
Range	0%-2%	0%-2%	0%-2%
Overall Historical Incidence: All Routes			
Total (%)	6/1,448 (0.4%)	1/1,448 (0.1%)	7/1,448 (0.5%)
Mean ± standard deviation	0.5% ± 0.9%	0.1% ± 0.4%	0.5% ± 0.9%
Range	0%-2%	0%-2%	0%-2%

[a] Data as of January 28, 2005

Table A4b
Historical Incidence of Brain Neoplasms in Control Male F344/N Rats[a]

Study	Incidence in Controls: Malignant Astrocytoma	Incidence in Controls: Malignant Oligodendroglioma	Incidence in Controls: Astrocytoma, Glioma, or Oligodendroglioma[b]
Historical Incidence: Inhalation Studies			
Decalin	0/50	0/50	0/50
Divinylbenzene	0/49	0/49	0/49
Indium phosphide	0/50	0/50	0/50
Methyl isobutyl ketone	0/50	0/50	0/50
Naphthalene	0/49	0/49	0/49
Propylene glycol mono-*t*-butyl ether	0/50	0/50	0/50
Stoddard solvent IIC	1/50	0/50	1/50
Vanadium pentoxide	0/50	0/50	0/50
Overall Historical Incidence: Inhalation Studies			
Total (%)	1/398 (0.3%)	0/398 (0.0%)	1/398 (0.3%)
Mean ± standard deviation	0.3% ± 0.7%		0.3% ± 0.7%
Range	0%-2%		0%-2%
Overall Historical Incidence: All Routes			
Total (%)	4/1,458 (0.3%)	1/1,458 (0.1%)	8/1,458 (0.6%)
Mean ± standard deviation	0.3% ± 0.7%	0.0% ± 0.2%	0.5% ± 1.1%
Range	0%-2%	0%-1%	0%-4%

[a] Data as of January 28, 2005

[b] Includes malignant astrocytoma, malignant glioma, and benign and malignant oligodendroglioma

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	15	9	12	13
Natural deaths	4	6	6	5
Survivors				
Died last week of the study			1	
Terminal sacrifice	31	35	31	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Foreign body				1 (2%)
Intestine small, jejunum	(46)	(47)	(47)	(46)
Necrosis		1 (2%)		
Intestine small, ileum	(46)	(47)	(45)	(46)
Dilatation		1 (2%)		
Liver	(50)	(49)	(50)	(50)
Angiectasis			1 (2%)	1 (2%)
Clear cell focus	2 (4%)	5 (10%)	1 (2%)	1 (2%)
Hemorrhage	1 (2%)			
Hepatodiaphragmatic nodule	2 (4%)	2 (4%)	4 (8%)	8 (16%)
Inflammation, granulomatous		1 (2%)		
Necrosis	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Vacuolization cytoplasmic	1 (2%)	2 (4%)	3 (6%)	3 (6%)
Bile duct, hyperplasia			3 (6%)	
Hepatocyte, regeneration			1 (2%)	
Periportal, inflammation, chronic			2 (4%)	
Serosa, fibrosis		1 (2%)		1 (2%)
Serosa, hemorrhage				1 (2%)
Mesentery	(12)	(13)	(18)	(11)
Necrosis	7 (58%)	13 (100%)	18 (100%)	9 (82%)
Fat, hemorrhage				1 (9%)
Oral mucosa	(1)		(1)	(4)
Gingival, cyst				1 (25%)
Gingival, hyperplasia, squamous	1 (100%)			
Pancreas	(50)	(49)	(50)	(50)
Thrombosis			1 (2%)	
Acinus, atrophy	15 (30%)	18 (37%)	27 (54%)	21 (42%)
Acinus, hyperplasia			1 (2%)	
Acinus, inflammation		1 (2%)		
Duct, cyst	1 (2%)	2 (4%)	3 (6%)	
Stomach, forestomach	(50)	(48)	(50)	(50)
Diverticulum		1 (2%)		
Hyperplasia, squamous	1 (2%)			
Inflammation, suppurative		1 (2%)		
Ulcer	4 (8%)	1 (2%)	1 (2%)	
Stomach, glandular	(50)	(48)	(50)	(49)
Erosion		2 (4%)	2 (4%)	2 (4%)
Ulcer	1 (2%)	2 (4%)	1 (2%)	
Epithelium, hyperplasia				1 (2%)
Tongue	(1)	(1)		
Epithelium, hyperplasia		1 (100%)		

[a] Number of animals examined microscopically at the site and the number of animals with lesion

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Thrombosis	1 (2%)			
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	7 (14%)	5 (10%)	1 (2%)	1 (2%)
Atrium, thrombosis	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Pericardium, inflammation			1 (2%)	
Pericardium, pigmentation			1 (2%)	
Pericardium, epicardium, infiltration cellular, histiocyte		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)			2 (4%)
Necrosis		2 (4%)		
Vacuolization cytoplasmic	8 (16%)	8 (16%)	7 (14%)	6 (12%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	12 (24%)	13 (26%)	8 (16%)	14 (28%)
Bilateral, hyperplasia				1 (2%)
Islets, pancreatic	(50)	(48)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Parathyroid gland	(46)	(48)	(49)	(47)
Hyperplasia	1 (2%)	1 (2%)		
Pituitary gland	(50)	(50)	(50)	(49)
Cyst	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hemorrhage	1 (2%)			1 (2%)
Pars distalis, hematocyst		1 (2%)		
Pars distalis, hyperplasia	5 (10%)	8 (16%)	9 (18%)	8 (16%)
Thyroid gland	(50)	(50)	(50)	(49)
C-cell, hyperplasia	2 (4%)	4 (8%)	9 (18%)	7 (14%)
Follicular cell, hyperplasia		2 (4%)	2 (4%)	1 (2%)
General Body System				
None				
Genital System				
Penis			(2)	
Inflammation			1 (50%)	
Preputial gland	(48)	(50)	(50)	(49)
Cyst	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Hyperplasia	1 (2%)	4 (8%)	1 (2%)	1 (2%)
Prostate	(50)	(50)	(50)	(50)
Hyperplasia			1 (2%)	
Inflammation, suppurative	5 (10%)	1 (2%)	4 (8%)	2 (4%)
Seminal vesicle	(50)	(49)	(50)	(50)
Dilatation				1 (2%)
Hyperplasia		1 (2%)		
Inflammation, suppurative	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Artery, inflammation, chronic active			2 (4%)	
Germinal epithelium, atrophy	16 (32%)	12 (24%)	11 (22%)	9 (18%)
Interstitial cell, hyperplasia	7 (14%)	6 (12%)	2 (4%)	3 (6%)

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Hematopoietic System				
Lymph node	(11)	(5)	(11)	(6)
Deep cervical, angiectasis	1 (9%)			1 (17%)
Deep cervical, cyst		1 (20%)		
Deep cervical, hemorrhage			1 (9%)	
Deep cervical, hyperplasia, lymphoid	1 (9%)			
Pancreatic, ectasia			1 (9%)	
Pancreatic, hemorrhage				1 (17%)
Pancreatic, infiltration cellular, histiocyte			1 (9%)	
Lymph node, bronchial	(7)	(6)	(12)	(5)
Hemorrhage				1 (20%)
Infiltration cellular				1 (20%)
Pigmentation				1 (20%)
Lymph node, mesenteric	(49)	(49)	(50)	(50)
Angiectasis	1 (2%)			
Ectasia		1 (2%)		
Hemorrhage				1 (2%)
Hyperplasia, lymphoid			1 (2%)	
Infiltration cellular, histiocyte	1 (2%)		1 (2%)	3 (6%)
Lymph node, mediastinal	(19)	(23)	(25)	(38)
Angiectasis				1 (3%)
Hyperplasia, lymphoid				1 (3%)
Spleen	(50)	(49)	(50)	(50)
Accessory spleen		3 (6%)		1 (2%)
Fibrosis	2 (4%)	6 (12%)	4 (8%)	1 (2%)
Hematopoietic cell proliferation				1 (2%)
Hemorrhage		2 (4%)	1 (2%)	1 (2%)
Hyperplasia, focal, lymphoid		1 (2%)		
Necrosis	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Lymphocyte, hyperplasia, diffuse	1 (2%)			
Thymus	(48)	(44)	(46)	(42)
Hemorrhage			1 (2%)	
Integumentary System				
Mammary gland	(35)	(43)	(47)	(48)
Galactocele	3 (9%)	2 (5%)	6 (13%)	3 (6%)
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	4 (8%)	1 (2%)	3 (6%)	2 (4%)
Hyperkeratosis	2 (4%)	1 (2%)	2 (4%)	
Inflammation, acute			2 (4%)	
Inflammation, granulomatous				1 (2%)
Ulcer			2 (4%)	
Subcutaneous tissue, thrombosis			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis			1 (2%)	
Cartilage, femur, hyperplasia	1 (2%)			
Femur, fracture		1 (2%)		

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Nervous System				
Brain	(49)	(50)	(50)	(50)
Compression	10 (20%)	5 (10%)	8 (16%)	6 (12%)
Gliosis				1 (2%)
Hemorrhage		1 (2%)	1 (2%)	
Respiratory System				
Larynx	(49)	(49)	(50)	(49)
Foreign body	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Inflammation, suppurative		1 (2%)	1 (2%)	1 (2%)
Epiglottis, metaplasia, squamous			1 (2%)	1 (2%)
Lung	(50)	(50)	(50)	(50)
Congestion				1 (2%)
Hemorrhage	2 (4%)	1 (2%)	4 (8%)	4 (8%)
Inflammation, chronic			1 (2%)	
Inflammation, chronic, diffuse			1 (2%)	
Inflammation, chronic, focal	4 (8%)	4 (8%)	5 (10%)	14 (28%)
Inflammation, suppurative	1 (2%)			
Necrosis	1 (2%)		1 (2%)	
Thrombosis	1 (2%)			
Alveolar epithelium, hyperplasia	4 (8%)	8 (16%)	6 (12%)	6 (12%)
Alveolar epithelium, hypertrophy		1 (2%)	1 (2%)	2 (4%)
Alveolus, hypertrophy				1 (2%)
Alveolus, infiltration cellular, focal, histiocyte	9 (18%)	12 (24%)	11 (22%)	4 (8%)
Interstitium, fibrosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Mediastinum, abscess	1 (2%)			
Mediastinum, inflammation, chronic			1 (2%)	
Mediastinum, pigmentation			1 (2%)	
Perivascular, edema				1 (2%)
Perivascular, infiltration cellular, eosinophil				1 (2%)
Nose	(50)	(48)	(50)	(49)
Foreign body	5 (10%)	1 (2%)	3 (6%)	
Inflammation, suppurative	5 (10%)	9 (19%)	17 (34%)	10 (20%)
Glands, dilatation	3 (6%)	30 (63%)	48 (96%)	46 (94%)
Goblet cell, hyperplasia	1 (2%)	3 (6%)	7 (14%)	16 (33%)
Nasolacrimal duct, inflammation, suppurative	2 (4%)	6 (13%)	1 (2%)	4 (8%)
Nasopharyngeal duct, cyst				1 (2%)
Nasopharyngeal duct, foreign body				1 (2%)
Nasopharyngeal duct, inflammation, suppurative			1 (2%)	
Nasopharyngeal duct, respiratory epithelium, hyperplasia				1 (2%)
Olfactory epithelium, degeneration		47 (98%)	49 (98%)	49 (100%)
Olfactory epithelium, degeneration, hyaline	4 (8%)		2 (4%)	1 (2%)
Olfactory epithelium, hyperplasia, basal cell		21 (44%)	44 (88%)	48 (98%)
Olfactory epithelium, metaplasia		1 (2%)		2 (4%)
Respiratory epithelium, hyperplasia	1 (2%)			
Turbinate, cyst		1 (2%)		
Pleura	(50)	(50)	(50)	(50)
Mesothelium, hyperplasia			1 (2%)	
Trachea	(50)	(49)	(50)	(49)
Glands, degeneration, cystic	1 (2%)			5 (10%)

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Special Senses System				
Eye	(50)	(48)	(48)	(49)
Anterior chamber, hemorrhage			1 (2%)	
Cornea, mineralization				1 (2%)
Lens, cataract	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Retina, atrophy		1 (2%)		
Harderian gland	(50)	(50)	(50)	(50)
Atrophy			1 (2%)	
Zymbal's gland	(1)		(3)	
Inflammation, suppurative			1 (33%)	
Urinary System				
Kidney	(50)	(49)	(50)	(49)
Cyst		1 (2%)		1 (2%)
Nephropathy, chronic	37 (74%)	41 (84%)	41 (82%)	45 (92%)
Cortex, infarct	1 (2%)	1 (2%)		
Cortex, renal tubule, degeneration				1 (2%)
Cortex, renal tubule, hyperplasia	1 (2%)	2 (4%)		2 (4%)
Cortex, renal tubule, hypertrophy	1 (2%)			
Medulla, infarct		1 (2%)		
Medulla, infiltration cellular, lipocyte		1 (2%)		
Papilla, renal tubule, dilatation				1 (2%)
Pelvis, transitional epithelium, hyperplasia	1 (2%)	1 (2%)		
Pelvis, transitional epithelium, mineralization				1 (2%)
Urethra			(1)	
Transitional epithelium, hyperplasia			1 (100%)	
Urinary bladder	(50)	(49)	(50)	(49)
Calculus microscopic observation only	4 (8%)	2 (4%)	4 (8%)	4 (8%)
Hemorrhage	2 (4%)	1 (2%)	1 (2%)	
Transitional epithelium, hyperplasia			1 (2%)	

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF DIVINYLBENZENE-HP

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Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death		1		
Moribund	10	16	14	26
Natural deaths	7	3	3	2
Survivors				
Terminal sacrifice	33	30	33	22
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Carcinoma, metastatic, Zymbal's gland	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Hepatocellular carcinoma			1 (2%)	
Hepatocellular adenoma		2 (4%)		
Hepatocellular adenoma, multiple			2 (4%)	
Histiocytic sarcoma, metastatic, spleen	1 (2%)			
Mesentery	(15)	(20)	(17)	(6)
Carcinoma, metastatic, liver			1 (6%)	
Pancreas	(50)	(49)	(50)	(50)
Tongue	(1)	(1)	(3)	(3)
Squamous cell papilloma		1 (100%)		1 (33%)
Cardiovascular System				
None				
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Carcinoma				1 (2%)
Carcinoma, metastatic, mammary gland		1 (2%)		
Carcinoma, metastatic, Zymbal's gland	1 (2%)			
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant			1 (2%)	1 (2%)
Pheochromocytoma benign	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Bilateral, pheochromocytoma benign				1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	1 (2%)		1 (2%)	1 (2%)
Carcinoma				1 (2%)
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	37 (74%)	34 (68%)	39 (78%)	28 (56%)
Thyroid gland	(50)	(50)	(50)	(50)
Carcinoma, metastatic, Zymbal's gland	1 (2%)			
C-cell, adenoma		5 (10%)	1 (2%)	4 (8%)
C-cell, carcinoma	1 (2%)	1 (2%)	1 (2%)	
General Body System				
None				

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Genital System				
Clitoral gland	(50)	(50)	(50)	(50)
Carcinoma			1 (2%)	
Ovary	(50)	(50)	(50)	(50)
Granulosa cell tumor benign		1 (2%)		
Uterus	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Carcinoma				1 (2%)
Polyp stromal	9 (18%)	6 (12%)	8 (16%)	6 (12%)
Sarcoma stromal		1 (2%)		
Schwannoma malignant		1 (2%)		
Bilateral, polyp stromal				1 (2%)
Cervix, sarcoma stromal		1 (2%)		
Vagina		(2)		(3)
Sarcoma		1 (50%)		
Hematopoietic System				
Lymph node	(6)	(10)	(9)	(8)
Deep cervical, carcinoma, metastatic, Zymbal's gland	1 (17%)			
Pancreatic, carcinoma, metastatic, mammary gland		1 (10%)		
Pancreatic, histiocytic sarcoma, metastatic, spleen	1 (17%)			
Lymph node, bronchial	(8)	(9)	(5)	(14)
Lymph node, mandibular	(3)	(1)	(5)	(3)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Lymph node, mediastinal	(32)	(37)	(44)	(34)
Carcinoma, metastatic, mammary gland		1 (3%)		
Carcinoma, metastatic, Zymbal's gland	1 (3%)			
Spleen	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Thymus	(45)	(41)	(46)	(39)
Thymoma malignant			1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Carcinoma	3 (6%)	4 (8%)	3 (6%)	
Carcinoma, multiple		1 (2%)	1 (2%)	
Fibroadenoma	14 (28%)	14 (28%)	13 (26%)	9 (18%)
Fibroadenoma, multiple	6 (12%)	8 (16%)	6 (12%)	5 (10%)
Skin	(50)	(50)	(50)	(50)
Basal cell carcinoma		1 (2%)		
Subcutaneous tissue, histiocytic sarcoma	1 (2%)			
Subcutaneous tissue, lipoma			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Femur, osteosarcoma				1 (2%)
Vertebra, osteosarcoma		1 (2%)		

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)	
Respiratory System				
Larynx	(50)	(50)	(49)	(50)
Carcinoma, metastatic, thyroid gland	1 (2%)			
Carcinoma, metastatic, Zymbal's gland	1 (2%)			
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma				2 (4%)
Carcinoma, metastatic, liver			1 (2%)	
Carcinoma, metastatic, mammary gland		1 (2%)		
Carcinoma, metastatic, thyroid gland			1 (2%)	
Carcinoma, metastatic, Zymbal's gland	1 (2%)			
Osteosarcoma, metastatic, bone		1 (2%)		1 (2%)
Nose	(50)	(50)	(49)	(49)
Respiratory epithelium, adenoma				1 (2%)
Pleura	(50)	(50)	(50)	(49)
Osteosarcoma, metastatic, bone				1 (2%)
Trachea	(50)	(50)	(50)	(50)
Carcinoma, metastatic, Zymbal's gland	1 (2%)			
Special Senses System				
Eye	(50)	(48)	(49)	(49)
Carcinoma, metastatic, Zymbal's gland	1 (2%)			
Harderian gland	(50)	(50)	(50)	(50)
Adenoma				1 (2%)
Carcinoma, metastatic, Zymbal's gland	1 (2%)			
Zymbal's gland	(1)			(2)
Carcinoma	1 (100%)			2 (100%)
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Osteosarcoma, metastatic, bone				1 (2%)
Urinary bladder	(50)	(50)	(49)	(49)
Transitional epithelium, carcinoma			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)			
Leukemia mononuclear	10 (20%)	18 (36%)	22 (44%)	22 (44%)

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	46	46	49	47
Total primary neoplasms	87	104	107	90
Total animals with benign neoplasms	43	42	45	36
Total benign neoplasms	70	74	74	61
Total animals with malignant neoplasms	17	27	28	27
Total malignant neoplasms	17	30	33	29
Total animals with metastatic neoplasms	3	2	2	1
Total metastatic neoplasms	13	5	3	3

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	436	437	437	455	477	501	515	533	549	625	631	687	694	703	710	716	722	731	731	731	731	731	731	731	732
Carcass ID Number	137	119	134	109	103	132	124	117	123	135	139	122	144	116	126	101	115	125	127	131	138	141	142	146	106
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland												X													
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	+	+	+	+	+	+	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, spleen								X																	
Mesentery		+				+	+			+	+							+	+						
Oral mucosa			+																						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland												X													
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																			X			X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X	X	X		X	X	X		X	X		X	X	X	X	X	X	X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland												X													
C-cell, carcinoma																X									
General Body System																									
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Polyp stromal												X		X									X		

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	
Carcass ID Number	107	108	110	111	113	114	118	120	121	128	129	130	133	136	140	145	147	150	102	104	105	112	143	148	149	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, spleen																										1
Mesentery			+			+	+		+			+			+	+									+	15
Oral mucosa																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue										+																1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X		X		X	X	X	X	X		X		X	X		X	X	X	X		X	X	37
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
C-cell, carcinoma																										1
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Polyp stromal			X				X			X			X					X						X		9

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	4 3 6	4 3 7	4 3 7	4 5 5	4 7 1	5 0 1	5 1 5	5 3 3	5 4 9	6 2 5	6 3 1	6 8 7	6 9 4	7 0 3	7 1 0	7 1 6	7 2 2	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2
Carcass ID Number	1 3 7	1 1 9	1 3 4	1 0 9	1 0 3	1 3 2	1 2 4	1 1 7	1 2 3	1 3 5	1 3 9	1 2 2	1 4 4	1 1 6	1 2 6	1 0 1	1 1 5	1 2 5	1 2 7	1 3 1	1 3 8	1 4 1	1 4 2	1 4 6	1 0 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+			+	+			+										
Deep cervical, carcinoma, metastatic, Zymbal's gland												X													
Pancreatic, histiocytic sarcoma, metastatic, spleen								X																	
Lymph node, bronchial	M	+	M	M	M	M	M	M	M	+	+	M	M	+	M	M	M	+	M	M	M	M	M	+	M
Lymph node, mandibular	M	M	M	M	M	+	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	M	M	+	+	M	+	M	M
Carcinoma, metastatic, Zymbal's gland												X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Thymus	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																							X	X	
Fibroadenoma											X		X			X	X		X			X		X	
Fibroadenoma, multiple														X											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, histiocytic sarcoma	X																								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																X									
Carcinoma, metastatic, Zymbal's gland												X													
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland												X													

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	
Carcass ID Number	107	108	110	111	113	114	118	120	121	128	129	130	133	136	140	145	147	150	102	104	105	112	143	148	149	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node									+							+										6
Deep cervical, carcinoma, metastatic, Zymbal's gland																										1
Pancreatic, histiocytic sarcoma, metastatic, spleen																										1
Lymph node, bronchial	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	8
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	M	M	+	M	M	M	+	M	32
Carcinoma, metastatic, Zymbal's gland																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																								X		3
Fibroadenoma			X	X	X				X					X				X	X							14
Fibroadenoma, multiple		X					X				X				X							X				6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, histiocytic sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle								+	+																	2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve									+																	1
Spinal cord									+																	1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Carcinoma, metastatic, Zymbal's gland																										1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	436	437	437	455	477	501	515	533	549	625	631	687	694	703	710	716	722	731	731	731	731	731	731	731	732
Carcass ID Number	137	119	134	109	103	132	124	117	123	135	139	122	144	116	126	101	115	125	127	131	138	141	142	146	106
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland												X													
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland												X													
Zymbal's gland												+													
Carcinoma												X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X							X																	
Leukemia mononuclear					X						X			X	X										

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	
Carcass ID Number	107	108	110	111	113	114	118	120	121	128	129	130	133	136	140	145	147	150	102	104	105	112	143	148	149	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Leukemia mononuclear							X		X	X				X		X									X	10

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	374	487	506	542	543	561	617	638	642	666	670	670	688	696	703	703	708	711	715	729	731	731	731	732	732
Carcass ID Number	340	315	345	311	334	330	320	342	308	331	318	337	321	309	332	333	349	348	314	343	305	312	328	302	303
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X																		
Mesentery					+	+	+	+	+	+								+						+	
Pancreas	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																			+						
Squamous cell papilloma																			X						
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland	X																								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign														X											
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X						X	X	X	X	X			X	X	X	X	X		X	X	X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma			X						X																
C-cell, carcinoma													X												
General Body System																									
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal												X	X	X										X	
Sarcoma stromal						X																			
Schwannoma malignant					X																				
Cervix, sarcoma stromal																									
Vagina													+												
Sarcoma																									

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	304	306	313	317	319	322	324	329	335	336	338	341	350	301	307	310	316	323	325	326	327	339	344	346	347	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X																							2
Mesentery	+		+		+					+		+	+		+		+	+	+	+			+			20
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign									X																	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X			X			X			X	X	X	X	X			X	X	X	X	X	34
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma												X	X								X					5
C-cell, carcinoma																										1
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign												X														1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																				X	X					6
Sarcoma stromal																										1
Schwannoma malignant																										1
Cervix, sarcoma stromal									X																	1
Vagina									+																	2
Sarcoma									X																	1

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	374	487	506	542	543	561	617	638	642	666	670	678	688	696	703	703	708	711	715	729	731	731	731	732	732
Carcass ID Number	340	315	345	311	334	330	320	342	308	331	318	337	321	309	332	333	349	348	314	343	305	312	328	302	303
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+											+		+		+			+			+	+		
Pancreatic, carcinoma, metastatic, mammary gland	X																								
Lymph node, bronchial	M	M	M	M	M	M	+	+	M	M	M	+	M	M	M	+	+	M	M	M	M	M	M	M	M
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+
Carcinoma, metastatic, mammary gland	X																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Carcinoma	X															X			X						X
Carcinoma, multiple																									
Fibroadenoma							X	X		X	X			X			X	X	X						
Fibroadenoma, multiple									X											X	X		X		X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, osteosarcoma		X																							
Skeletal muscle								+								+									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve								+																	
Spinal cord		I						+																	
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland	X																								
Osteosarcoma, metastatic, bone		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye	+	+	+	I	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lacrimal gland																									

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Total
Carcass ID Number	0	0	1	1	1	2	2	2	3	3	3	4	5	0	0	1	1	2	2	2	2	3	4	4	4	Tissues/
	4	6	3	7	9	2	4	9	5	6	8	1	0	1	7	0	6	3	5	6	7	9	4	6	7	Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+							+																	10
Pancreatic, carcinoma, metastatic, mammary gland																										1
Lymph node, bronchial	M	M	M	M	+	M	+	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	+	M	M	9
Lymph node, mandibular	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	M	+	+	+	M	+	M	+	M	+	+	+	M	+	+	+	M	M	M	+	+	+	+	37
Carcinoma, metastatic, mammary gland																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	M	M	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	41
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										4
Carcinoma, multiple																		X								1
Fibroadenoma	X							X						X						X		X			X	14
Fibroadenoma, multiple																X	X	X								8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																					X					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, osteosarcoma																										1
Skeletal muscle		+																								3
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve		+																								2
Spinal cord		+																								2
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																										1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear															+											1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lacrimal gland																+										1

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

	3	4	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	7	8	0	4	4	6	1	3	4	6	7	7	8	9	0	0	0	1	1	2	3	3	3	3	3
	4	7	6	2	3	1	7	8	2	6	0	0	8	6	3	3	8	1	5	9	1	1	1	2	2
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Carcass ID Number	4	1	4	1	3	3	2	4	0	3	1	3	2	0	3	3	4	4	1	4	0	1	2	0	0
	0	5	5	1	4	0	0	2	8	1	8	7	1	9	2	3	9	8	4	3	5	2	8	2	3
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X	X	X	X			X		X	X			X		X		X	X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	304	306	313	317	319	322	324	329	335	336	338	341	350	301	307	310	316	323	325	326	327	339	344	346	347	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X	X					X			X		X						X						18

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 200 ppm

	3	4	4	4	5	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	7	8	9	9	0	8	8	1	5	6	7	0	1	1	1	2	2	3	3	3	3	3	3	3	3
	4	1	3	7	0	2	6	4	4	6	3	4	1	2	5	2	6	1	1	1	1	1	2	2	2
	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Carcass ID Number	1	0	4	2	1	0	3	5	1	2	4	4	2	3	1	2	1	0	0	2	3	3	0	0	0
	9	9	9	7	6	5	0	0	4	2	4	6	1	5	0	0	3	2	8	8	1	7	1	4	7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma													X												
Hepatocellular adenoma, multiple																									
Mesentery				+									+	+	+			+	+		+		+		+
Carcinoma, metastatic, liver													X												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																+									
Tooth	+																								
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant				X																					
Pheochromocytoma benign																						X			X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma															X										
General Body System																									
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																X									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal		X				X							X						X					X	

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 200 ppm

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	523	524	525	526	529	532	533	534	538	540	541	542	545	547	548	503	506	511	512	515	517	518	536	539	543	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma, multiple		X																					X			2
Mesentery	+				+							+	+	+					+				+		+	17
Carcinoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue				+											+											3
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign																				X						3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																			X							1
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X	X	X	X	X		X			X	X	X	X	X		X		X	X		X	39
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																				X						1
C-cell, carcinoma																										1
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X				X																X					8

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 200 ppm

Number of Days on Study	374	481	493	497	500	582	586	614	654	666	673	704	711	712	715	722	726	731	731	731	731	731	732	732	732
Carcass ID Number	519	509	549	527	516	505	530	550	514	522	544	546	521	535	510	520	513	502	508	528	531	537	501	504	507
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+						+	+				+	+					+			
Lymph node, bronchial	M	M	M	M	+	M	M	M	M	+	M	+	M	M	+	M	M	M	M	M	M	M	M	M	M
Lymph node, mandibular	M	M	M	M	M	M	M	+	M	M	M	M	M	+	+	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Carcinoma, multiple																									
Fibroadenoma										X	X		X	X			X	X	X			X			
Fibroadenoma, multiple															X					X	X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle											+		+	+							+				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant	X																								
Peripheral nerve											+		+								+				
Spinal cord											+		+								+				
Respiratory System																									
Larynx	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, liver													X												
Carcinoma, metastatic, thyroid gland															X										
Nose	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear															+										
Eye	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 200 ppm

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	523	524	525	526	529	532	533	534	538	540	541	542	545	547	548	503	506	511	512	515	517	518	536	539	543	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+												+												9
Lymph node, bronchial	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	5
Lymph node, mandibular	M	M	M	M	M	+	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	5
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thymoma malignant									X																	1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma					X	X																X				3
Carcinoma, multiple									X																	1
Fibroadenoma							X			X	X		X											X		13
Fibroadenoma, multiple	X				X																	X				6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, lipoma																							X			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle						+											+					+				7
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Peripheral nerve						+											+					+				6
Spinal cord						+											+					+				6
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, liver																										1
Carcinoma, metastatic, thyroid gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																	+									2
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 200 ppm

	3	4	4	4	5	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	7	8	9	9	0	8	8	1	5	6	7	0	1	1	1	2	2	3	3	3	3	3	3	3	3
	4	1	3	7	0	2	6	4	4	6	3	4	1	2	5	2	6	1	1	1	1	1	2	2	2
	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Carcass ID Number	1	0	4	2	1	0	3	5	1	2	4	4	2	3	1	2	1	0	0	2	3	3	0	0	0
	9	9	9	7	6	5	0	0	4	2	4	6	1	5	0	0	3	2	8	8	1	7	1	4	7
Urinary System																									
Kidney	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma								X																	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X					X	X	X	X	X	X		X					X	X		X

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 200 ppm

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	523	524	525	526	529	532	533	534	538	540	541	542	545	547	548	503	506	511	512	515	517	518	536	539	543	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, carcinoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X			X	X								X	X					X	X		X		X	22

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 400 ppm

Number of Days on Study	151	516	523	525	529	535	535	540	551	563	586	586	589	600	600	613	617	626	626	631	653	653	656	656	684
Carcass ID Number	721	732	712	746	701	703	741	749	706	723	726	733	717	716	730	709	729	708	713	748	711	719	702	739	720
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery							+									+									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue										+														+	
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant													X												
Pheochromocytoma benign																								X	
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																						
Carcinoma						X																			
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X		X		X		X	X	X	X							X		X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X														X	
General Body System																									
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Polyp stromal													X										X		
Bilateral, polyp stromal																									X
Vagina	+								+																+

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 400 ppm

Number of Days on Study	708	708	712	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	
Carcass ID Number	725	731	714	704	724	728	737	740	742	705	710	718	727	734	735	736	738	743	744	750	707	715	722	745	747	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery										+			+			+								+		6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																					+					3
Squamous cell papilloma																					X					1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma															X											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign																										1
Bilateral, pheochromocytoma benign	X																									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X			X	X	X	X	X	X	X		X	X	X	X	X	X	X		X		X		28
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma									X								X									4
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma													X													1
Polyp stromal								X		X									X						X	6
Bilateral, polyp stromal																										1
Vagina																										3

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 400 ppm

	1	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6
Number of Days on Study	5	1	2	2	2	3	3	4	5	6	8	8	8	0	0	1	1	2	2	3	5	5	5	5	8
	1	6	3	5	9	5	5	0	1	3	6	6	9	0	0	3	7	6	6	1	3	3	6	6	4
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Carcass ID Number	2	3	1	4	0	0	4	4	0	2	2	3	1	1	3	0	2	0	1	4	1	1	0	3	2
	1	2	2	6	1	3	1	9	6	3	6	3	7	6	0	9	9	8	3	8	1	9	2	9	0
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+															+		+	+		+	
Lymph node, bronchial	M	M	+	+	M	M	M	+	M	M	M	+	+	M	+	+	+	+	M	M	M	+	+	M	M
Lymph node, mandibular	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	M	M	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	M	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma			X							X				X									X		
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma																									
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Osteosarcoma, metastatic, bone																									
Nose	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory epithelium, adenoma																									
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Lacrimal gland																									
Zymbal's gland																	+								
Carcinoma																	X								

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 400 ppm

Number of Days on Study	708	708	712	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	
Carcass ID Number	725	731	714	704	724	728	737	740	742	705	710	718	727	734	735	736	738	743	744	750	707	715	722	745	747	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+																						+		8
Lymph node, bronchial	M	M	M	M	M	M	+	M	M	M	+	M	M	+	M	M	M	M	M	M	M	M	M	M	M	14
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	+	M	M	M	M	3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	M	M	M	+	M	+	+	M	+	M	+	+	+	+	+	+	M	+	M	+	M	+	34
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	M	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	39
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma				X								X	X							X					X	9
Fibroadenoma, multiple	X		X			X											X		X							5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femur, osteosarcoma							X																			1
Skeletal muscle						+			+			+			+				+							5
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve						+			+			+			+				+							5
Spinal cord						+			+			+			+				+							5
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X			X													2
Osteosarcoma, metastatic, bone							X																			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory epithelium, adenoma							X																			1
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	49
Osteosarcoma, metastatic, bone							X																			1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						1
Lacrimal gland										+																1
Zymbal's gland																		+								2
Carcinoma																		X								2

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 400 ppm

Number of Days on Study	151	516	523	525	529	535	535	540	551	563	586	586	589	600	600	613	617	626	626	631	653	653	656	656	684
Carcass ID Number	721	732	712	746	701	703	741	749	706	723	726	733	717	716	730	709	729	708	713	748	711	719	702	739	720
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									
Urinary bladder	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X	X		X		X		X						X		X	X	X	X	X	X	X	

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP: 400 ppm

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	0	0	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	8	8	2	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	Total
Carcass ID Number	2	3	1	0	2	2	3	4	4	0	1	1	2	3	3	3	3	4	4	5	0	1	2	4	4	Tissues/
	5	1	4	4	4	8	7	0	2	5	0	8	7	4	5	6	8	3	4	0	7	5	2	5	7	Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone							X																			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X		X		X					X		X		X										22

Table B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	2/50 (4%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate[b]	4.7%	4.6%	6.8%	5.3%
Terminal rate[c]	2/33 (6%)	1/30 (3%)	3/33 (9%)	0/22 (0%)
First incidence (days)	731 (T)	696	731 (T)	656
Poly-3 test[d]	P=0.506	P=0.683N	P=0.516	P=0.656
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	2/50 (4%)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted rate	4.7%	4.6%	9.0%	7.8%
Terminal rate	2/33 (6%)	1/30 (3%)	3/33 (9%)	0/22 (0%)
First incidence (days)	731 (T)	696	497	589
Poly-3 test	P=0.300	P=0.683N	P=0.361	P=0.458
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	0/50 (0%)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	4.6%	6.8%	0.0%
Terminal rate	0/33 (0%)	1/30 (3%)	2/33 (6%)	0/22 (0%)
First incidence (days)	—[e]	617	711	—
Poly-3 test	P=0.596N	P=0.245	P=0.125	—[f]
Mammary Gland: Fibroadenoma				
Overall rate	20/50 (40%)	22/50 (44%)	19/50 (38%)	14/50 (28%)
Adjusted rate	46.5%	48.4%	42.7%	35.2%
Terminal rate	15/33 (46%)	12/30 (40%)	13/33 (39%)	8/22 (36%)
First incidence (days)	631	617	666	523
Poly-3 test	P=0.133N	P=0.512	P=0.441N	P=0.200N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	20/50 (40%)	23/50 (46%)	19/50 (38%)	14/50 (28%)
Adjusted rate	46.5%	50.4%	42.7%	35.2%
Terminal rate	15/33 (46%)	12/30 (40%)	13/33 (39%)	8/22 (36%)
First incidence (days)	631	617	666	523
Poly-3 test	P=0.119N	P=0.438	P=0.441N	P=0.200N
Mammary Gland: Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	4/50 (8%)	0/50 (0%)
Adjusted rate	7.1%	11.2%	9.1%	0.0%
Terminal rate	3/33 (9%)	2/30 (7%)	4/33 (12%)	0/22 (0%)
First incidence (days)	731 (T)	374	731 (T)	—
Poly-3 test	P=0.110N	P=0.385	P=0.520	P=0.140N
Mammary Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	6/50 (12%)	4/50 (8%)	0/50 (0%)
Adjusted rate	7.1%	13.4%	9.1%	0.0%
Terminal rate	3/33 (9%)	2/30 (7%)	4/33 (12%)	0/22 (0%)
First incidence (days)	731 (T)	374	731 (T)	—
Poly-3 test	P=0.093N	P=0.270	P=0.520	P=0.140N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	22/50 (44%)	25/50 (50%)	21/50 (42%)	14/50 (28%)
Adjusted rate	51.2%	53.6%	47.1%	35.2%
Terminal rate	17/33 (52%)	12/30 (40%)	15/33 (46%)	8/22 (36%)
First incidence (days)	631	374	666	523
Poly-3 test	P=0.057N	P=0.491	P=0.435N	P=0.099N

Table B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	37/50 (74%)	34/50 (68%)	39/50 (78%)	28/50 (56%)
Adjusted rate	79.1%	73.2%	82.5%	66.3%
Terminal rate	26/33 (79%)	22/30 (73%)	27/33 (82%)	16/22 (73%)
First incidence (days)	455	374	493	529
Poly-3 test	P=0.138N	P=0.330N	P=0.438	P=0.114N
Thyroid Gland (C-cell): Adenoma				
Overall rate	0/50 (0%)	5/50 (10%)	1/50 (2%)	4/50 (8%)
Adjusted rate	0.0%	11.2%	2.3%	10.4%
Terminal rate	0/33 (0%)	3/30 (10%)	1/33 (3%)	2/22 (9%)
First incidence (days)	—	506	731 (T)	563
Poly-3 test	P=0.134	P=0.035	P=0.507	P=0.049
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	6/50 (12%)	2/50 (4%)	4/50 (8%)
Adjusted rate	2.4%	13.4%	4.6%	10.4%
Terminal rate	0/33 (0%)	3/30 (10%)	1/33 (3%)	2/22 (9%)
First incidence (days)	716	506	715	563
Poly-3 test	P=0.282	P=0.064	P=0.512	P=0.150
Uterus: Stromal Polyp				
Overall rate	9/50 (18%)	6/50 (12%)	8/50 (16%)	7/50 (14%)
Adjusted rate	21.1%	13.6%	17.7%	18.1%
Terminal rate	7/33 (21%)	3/30 (10%)	5/33 (15%)	4/22 (18%)
First incidence (days)	687	670	481	589
Poly-3 test	P=0.501N	P=0.261N	P=0.447N	P=0.475N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	9/50 (18%)	8/50 (16%)	8/50 (16%)	7/50 (14%)
Adjusted rate	21.1%	17.9%	17.7%	18.1%
Terminal rate	7/33 (21%)	4/30 (13%)	5/33 (15%)	4/22 (18%)
First incidence (days)	687	561	481	589
Poly-3 test	P=0.430N	P=0.458N	P=0.447N	P=0.475N
All Organs: Mononuclear Cell Leukemia				
Overall rate	10/50 (20%)	18/50 (36%)	22/50 (44%)	22/50 (44%)
Adjusted rate	23.0%	38.9%	47.1%	49.7%
Terminal rate	6/33 (18%)	8/30 (27%)	12/33 (36%)	5/22 (23%)
First incidence (days)	477	542	481	516
Poly-3 test	P=0.008	P=0.078	P=0.013	P=0.007
All Organs: Benign Neoplasms				
Overall rate	43/50 (86%)	42/50 (84%)	45/50 (90%)	36/50 (72%)
Adjusted rate	91.6%	88.3%	93.7%	82.0%
Terminal rate	31/33 (94%)	26/30 (87%)	32/33 (97%)	20/22 (91%)
First incidence (days)	455	374	481	523
Poly-3 test	P=0.103N	P=0.418N	P=0.498	P=0.114N

Table B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
All Organs: Malignant Neoplasms				
Overall rate	17/50 (34%)	27/50 (54%)	28/50 (56%)	27/50 (54%)
Adjusted rate	37.6%	55.4%	57.5%	59.8%
Terminal rate	9/33 (27%)	11/30 (37%)	14/33 (42%)	8/22 (36%)
First incidence (days)	436	374	374	516
Poly-3 test	P=0.038	P=0.062	P=0.040	P=0.025
All Organs: Benign or Malignant Neoplasms				
Overall rate	46/50 (92%)	46/50 (92%)	49/50 (98%)	47/50 (94%)
Adjusted rate	95.0%	92.0%	98.0%	96.8%
Terminal rate	31/33 (94%)	26/30 (87%)	32/33 (97%)	21/22 (96%)
First incidence (days)	436	374	374	516
Poly-3 test	P=0.276	P=0.423N	P=0.391	P=0.528

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE B4
Historical Incidence of Mononuclear Cell Leukemia in Control Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence: Inhalation Studies	
Decalin	11/50
Divinylbenzene	10/50
Indium phosphide	14/50
Methyl isobutyl ketone	14/50
Naphthalene	16/49
Propylene glycol mono-*t*-butyl ether	24/50
Stoddard solvent IIC	26/50
Vanadium pentoxide	21/50
Overall Historical Incidence: Inhalation Studies	
Total (%)	136/399 (34.1%)
Mean ± standard deviation	34.1% ± 11.9%
Range	20%-52%
Overall Historical Incidence: All Routes	
Total (%)	383/1,459 (29.3%)
Mean ± standard deviation	26.7% ± 10.5%
Range	12%-52%

[a] Data as of January 28, 2005; includes data for lymphocytic, monocytic, monuclear cell, or undifferentiated leukemia.

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death		1		
Moribund	10	16	14	26
Natural deaths	7	3	3	2
Survivors				
Terminal sacrifice	33	30	33	22
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(49)	(49)	(50)
Epithelium, metaplasia, focal, squamous		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Clear cell focus	5 (10%)	7 (14%)	6 (12%)	
Hepatodiaphragmatic nodule	5 (10%)	7 (14%)	6 (12%)	9 (18%)
Necrosis			1 (2%)	
Vacuolization cytoplasmic	4 (8%)	3 (6%)		3 (6%)
Bile duct, hyperplasia			1 (2%)	
Hepatocyte, regeneration		1 (2%)	1 (2%)	
Periportal, inflammation, chronic	3 (6%)	2 (4%)	1 (2%)	2 (4%)
Portal, bile stasis	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Serosa, fibrosis			1 (2%)	
Mesentery	(15)	(20)	(17)	(6)
Necrosis	14 (93%)	20 (100%)	16 (94%)	6 (100%)
Oral mucosa	(1)			
Pharyngeal, ulcer	1 (100%)			
Pancreas	(50)	(49)	(50)	(50)
Acinus, atrophy	3 (6%)	5 (10%)	2 (4%)	4 (8%)
Salivary glands	(50)	(50)	(50)	(50)
Inflammation, chronic		1 (2%)		
Stomach, forestomach	(50)	(50)	(49)	(49)
Hyperplasia, focal, squamous		1 (2%)	1 (2%)	
Ulcer	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Stomach, glandular	(50)	(50)	(49)	(49)
Erosion			1 (2%)	1 (2%)
Ulcer			1 (2%)	
Epithelium, hyperplasia	1 (2%)			
Tongue	(1)	(1)	(3)	(3)
Epithelium, hyperplasia	1 (100%)		3 (100%)	2 (67%)
Tooth			(1)	
Peridontal tissue, inflammation			1 (100%)	
Pulp, inflammation, suppurative			1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy				3 (6%)
Atrium, thrombosis		1 (2%)	2 (4%)	
Pericardium, infiltration cellular, lymphoid				1 (2%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule			1 (2%)	
Hemorrhage		1 (2%)		
Hyperplasia				1 (2%)
Necrosis		1 (2%)		
Vacuolization cytoplasmic	14 (28%)	5 (10%)	7 (14%)	12 (24%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)	5 (10%)	2 (4%)
Parathyroid gland	(49)	(49)	(47)	(49)
Hyperplasia			1 (2%)	
Pituitary gland	(50)	(50)	(50)	(50)
Cyst	6 (12%)	6 (12%)	1 (2%)	5 (10%)
Pars distalis, angiectasis	1 (2%)			
Pars distalis, hematocyst				1 (2%)
Pars distalis, hyperplasia	4 (8%)	8 (16%)	4 (8%)	7 (14%)
Thyroid gland	(50)	(50)	(50)	(50)
Ultimobranchial cyst	1 (2%)			
C-cell, hyperplasia	5 (10%)	8 (16%)	6 (12%)	1 (2%)
Follicular cell, hyperplasia		1 (2%)		1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(50)	(50)	(50)	(50)
Cyst	3 (6%)		1 (2%)	
Hyperplasia	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Inflammation, chronic	2 (4%)	1 (2%)	1 (2%)	
Ovary	(50)	(50)	(50)	(50)
Cyst	5 (10%)	6 (12%)	11 (22%)	4 (8%)
Bilateral, cyst	1 (2%)			
Uterus	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
Necrosis		1 (2%)		
Endometrium, hyperplasia	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Myometrium, hyperplasia			1 (2%)	
Vagina		(2)		(3)
Inflammation, suppurative		1 (50%)		
Muscularis, hypertrophy				1 (33%)

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Myelofibrosis			1 (2%)	
Lymph node	(6)	(10)	(9)	(8)
Deep cervical, infiltration cellular, histiocyte		3 (30%)		1 (13%)
Pancreatic, pigmentation		1 (10%)	1 (11%)	
Lymph node, bronchial	(8)	(9)	(5)	(14)
Infiltration cellular, histiocyte				1 (7%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Infiltration cellular, histiocyte	2 (4%)	1 (2%)	2 (4%)	
Pigmentation				1 (2%)
Lymph node, mediastinal	(32)	(37)	(44)	(34)
Fibrosis			1 (2%)	
Hyperplasia, lymphoid	1 (3%)		1 (2%)	
Infiltration cellular, histiocyte	2 (6%)	1 (3%)		
Inflammation, suppurative	1 (3%)			
Spleen	(50)	(50)	(50)	(50)
Accessory spleen	2 (4%)	1 (2%)	1 (2%)	
Fibrosis	3 (6%)	1 (2%)	3 (6%)	1 (2%)
Hematopoietic cell proliferation		1 (2%)		
Hemorrhage	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Hyperplasia, focal, lymphoid		2 (4%)		
Inflammation, chronic active			1 (2%)	
Necrosis				1 (2%)
Thymus	(45)	(41)	(46)	(39)
Cyst				1 (3%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Galactocele	1 (2%)	2 (4%)		
Hyperplasia			1 (2%)	
Inflammation, chronic			1 (2%)	
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion		2 (4%)		1 (2%)
Hyperkeratosis		1 (2%)		
Inflammation, granulomatous				1 (2%)
Ulcer	1 (2%)		1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Joint, fracture		1 (2%)		
Tibia, fracture			1 (2%)	
Skeletal muscle	(2)	(3)	(7)	(5)
Inflammation, chronic		1 (33%)		
Necrosis	1 (50%)	1 (33%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	9 (18%)	10 (20%)	11 (22%)	7 (14%)
Congestion		1 (2%)		
Hemorrhage	2 (4%)	2 (4%)	6 (12%)	3 (6%)
Infarct			1 (2%)	

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Respiratory System				
Larynx	(50)	(50)	(49)	(50)
Foreign body		1 (2%)	3 (6%)	
Inflammation, suppurative		2 (4%)	1 (2%)	
Epiglottis, metaplasia, squamous	1 (2%)			
Lung	(50)	(50)	(50)	(50)
Atrophy	1 (2%)			
Cyst			1 (2%)	
Foreign body			1 (2%)	
Hemorrhage	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, histiocyte	1 (2%)			
Inflammation, chronic			1 (2%)	
Inflammation, chronic, diffuse	1 (2%)			1 (2%)
Inflammation, chronic, focal	27 (54%)	22 (44%)	26 (52%)	33 (66%)
Alveolar epithelium, hyperplasia	4 (8%)	2 (4%)	3 (6%)	1 (2%)
Alveolar epithelium, hypertrophy	1 (2%)	1 (2%)		1 (2%)
Alveolus, infiltration cellular, focal, histiocyte	8 (16%)	3 (6%)	6 (12%)	5 (10%)
Interstitium, fibrosis				1 (2%)
Mediastinum, necrosis, fatty	1 (2%)			
Nose	(50)	(50)	(49)	(49)
Foreign body	1 (2%)	5 (10%)	1 (2%)	
Inflammation, suppurative	5 (10%)	12 (24%)	8 (16%)	7 (14%)
Ulcer	1 (2%)			
Glands, dilatation		17 (34%)	38 (78%)	44 (90%)
Goblet cell, hyperplasia	1 (2%)	3 (6%)	1 (2%)	4 (8%)
Nasolacrimal duct, inflammation, suppurative	3 (6%)	1 (2%)	3 (6%)	1 (2%)
Nasopharyngeal duct, inflammation, suppurative			1 (2%)	
Olfactory epithelium, degeneration		50 (100%)	49 (100%)	48 (98%)
Olfactory epithelium, degeneration, hyaline	10 (20%)	14 (28%)	15 (31%)	4 (8%)
Olfactory epithelium, hyperplasia, basal cell		25 (50%)	42 (86%)	45 (92%)
Olfactory epithelium, regeneration, focal	1 (2%)			
Respiratory epithelium, degeneration, hyaline	5 (10%)	3 (6%)	4 (8%)	
Respiratory epithelium, hyperplasia	1 (2%)		1 (2%)	
Respiratory epithelium, metaplasia, squamous				1 (2%)
Pleura	(50)	(50)	(50)	(49)
Fibrosis	1 (2%)			
Infiltration cellular, lymphoid				1 (2%)
Trachea	(50)	(50)	(50)	(50)
Glands, degeneration, cystic			1 (2%)	1 (2%)
Special Senses System				
Eye	(50)	(48)	(49)	(49)
Atrophy			1 (2%)	
Inflammation, chronic	1 (2%)			
Anterior chamber, hemorrhage			1 (2%)	
Ciliary body, inflammation		1 (2%)		
Cornea, inflammation	1 (2%)			
Lens, cataract	1 (2%)	3 (6%)	4 (8%)	1 (2%)
Harderian gland	(50)	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)			

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	100 ppm	200 ppm	400 ppm
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Cyst			1 (2%)	
Nephropathy, chronic	19 (38%)	21 (42%)	19 (39%)	10 (20%)
Bilateral, cortex, renal tubule, degeneration				1 (2%)
Cortex, infarct				2 (4%)
Cortex, renal tubule, accumulation, hyaline droplet				1 (2%)
Cortex, renal tubule, hyperplasia	1 (2%)	1 (2%)		
Medulla, renal tubule, degeneration				1 (2%)
Pelvis, transitional epithelium, hyperplasia	1 (2%)			1 (2%)
Pelvis, transitional epithelium, mineralization	1 (2%)			
Renal tubule, dilatation	1 (2%)			
Urinary bladder	(50)	(50)	(49)	(49)
Transitional epithelium, hyperplasia	1 (2%)			

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF DIVINYLBENZENE-HP

TABLE C1 Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP C-2

TABLE C2 Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP C-6

TABLE C3 Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP C-28

TABLE C4 Historical Incidence of Alveolar/bronchiolar Neoplasms in Control Male $B6C3F_1$ Mice C-31

TABLE C5 Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP C-32

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	10 ppm	30 ppm	100 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	7	6	5	4
Natural deaths	2	6	3	3
Survivors				
Terminal sacrifice	41	38	42	43
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(42)	(34)	(42)	(45)
Adenoma	1 (2%)			
Intestine large, rectum	(48)	(45)	(46)	(47)
Leiomyosarcoma		1 (2%)		
Intestine large, cecum	(48)	(46)	(47)	(48)
Carcinoma		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Leiomyoma				1 (2%)
Polyp adenomatous	1 (2%)			
Intestine small, duodenum	(48)	(45)	(47)	(47)
Carcinoma		1 (2%)		
Intestine small, jejunum	(48)	(45)	(47)	(47)
Carcinoma	3 (6%)			4 (9%)
Intestine small, ileum	(48)	(45)	(47)	(47)
Carcinoma				1 (2%)
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas			1 (2%)	
Cholangiocarcinoma		1 (2%)		
Hemangiosarcoma	3 (6%)	1 (2%)		
Hepatoblastoma			2 (4%)	
Hepatocellular carcinoma	12 (24%)	9 (18%)	7 (14%)	7 (14%)
Hepatocellular carcinoma, multiple	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Hepatocellular adenoma	10 (20%)	12 (24%)	10 (20%)	11 (22%)
Hepatocellular adenoma, multiple	12 (24%)	5 (10%)	2 (4%)	1 (2%)
Hepatocholangiocarcinoma	1 (2%)	1 (2%)		
Histiocytic sarcoma				1 (2%)
Oral mucosa	(1)			
Pharyngeal, squamous cell carcinoma	1 (100%)			
Pancreas	(49)	(48)	(50)	(50)
Carcinoma			1 (2%)	
Stomach, forestomach	(49)	(50)	(49)	(50)
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Stomach, glandular	(48)	(48)	(47)	(49)
Carcinoma			1 (2%)	
Cardiovascular System				
Heart	(50)	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Hemangiosarcoma	2 (4%)			
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma	1 (2%)			

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Endocrine System				
Adrenal cortex	(49)	(49)	(50)	(50)
Adenoma		1 (2%)		
Capsule, adenoma	3 (6%)			
Adrenal medulla	(49)	(49)	(50)	(50)
Pheochromocytoma malignant			1 (2%)	
Pheochromocytoma benign	2 (4%)			
Islets, pancreatic	(49)	(48)	(50)	(50)
Adenoma	1 (2%)			
Thyroid gland	(49)	(49)	(50)	(50)
Follicular cell, adenoma		1 (2%)		
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Sarcoma	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Hemangioma		1 (2%)		
Interstitial cell, adenoma	1 (2%)	2 (4%)		1 (2%)
Hematopoietic System				
Bone marrow	(50)	(48)	(50)	(50)
Hemangiosarcoma	2 (4%)	1 (2%)		
Mast cell tumor malignant	1 (2%)			
Lymph node		(2)	(1)	
Iliac, leiomyosarcoma, metastatic, intestine large, rectum		1 (50%)		
Pancreatic, hepatocholangiocarcinoma, metastatic, liver		1 (50%)		
Lymph node, bronchial	(35)	(34)	(33)	(37)
Cholangiocarcinoma, metastatic, liver		1 (3%)		
Hepatocholangiocarcinoma, metastatic, liver		1 (3%)		
Histiocytic sarcoma	1 (3%)			
Lymph node, mandibular	(39)	(27)	(35)	(38)
Lymph node, mesenteric	(44)	(46)	(47)	(50)
Carcinoma, metastatic, pancreas			1 (2%)	
Hemangiosarcoma	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Lymph node, mediastinal	(37)	(38)	(33)	(29)
Carcinoma, metastatic, pancreas			1 (3%)	
Carcinoma, metastatic, intestine small, duodenum		1 (3%)		
Cholangiocarcinoma, metastatic, liver		1 (3%)		
Hepatocholangiocarcinoma, metastatic, liver		1 (3%)		
Histiocytic sarcoma	1 (3%)			
Mast cell tumor malignant, metastatic, bone marrow	1 (3%)			
Sarcoma, metastatic, skin	1 (3%)			
Spleen	(49)	(48)	(50)	(50)
Hemangiosarcoma	1 (2%)	2 (4%)		
Mast cell tumor malignant, metastatic, bone marrow	1 (2%)			
Squamous cell carcinoma, metastatic, stomach, Forestomach				1 (2%)
Thymus	(44)	(41)	(43)	(44)

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibrous histiocytoma	2 (4%)		1 (2%)	
Subcutaneous tissue, hemangioma		1 (2%)		1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)	1 (2%)		
Musculoskeletal System				
Skeletal muscle		(2)		
Cholangiocarcinoma, metastatic, liver		1 (50%)		
Hepatocholangiocarcinoma, metastatic, liver		1 (50%)		
Nervous System				
None				
Respiratory System				
Lung	(49)	(49)	(49)	(49)
Alveolar/bronchiolar adenoma	10 (20%)	5 (10%)	6 (12%)	13 (27%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)	1 (2%)		2 (4%)
Alveolar/bronchiolar carcinoma	5 (10%)	4 (8%)	2 (4%)	8 (16%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)	1 (2%)
Carcinoma, metastatic, pancreas			1 (2%)	
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Fibroma				1 (2%)
Hemangiosarcoma, metastatic, liver	1 (2%)	1 (2%)		
Hepatocellular carcinoma, metastatic, liver	6 (12%)	5 (10%)	3 (6%)	1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)		
Histiocytic sarcoma	1 (2%)			
Mast cell tumor malignant, metastatic, bone marrow	1 (2%)			
Sarcoma, metastatic, skin	1 (2%)			
Bronchus, adenoma				1 (2%)
Special Senses System				
Harderian gland	(50)	(49)	(50)	(50)
Adenoma	5 (10%)	3 (6%)	6 (12%)	7 (14%)
Carcinoma	1 (2%)	1 (2%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)		
Renal tubule, adenoma		1 (2%)		
Renal tubule, carcinoma	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			1 (2%)
Lymphoma malignant	1 (2%)		1 (2%)	1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	43	38	29	41
Total primary neoplasms	90	60	44	67
Total animals with benign neoplasms	35	24	21	27
Total benign neoplasms	49	34	25	47
Total animals with malignant neoplasms	26	21	14	23
Total malignant neoplasms	41	26	19	27
Total animals with metastatic neoplasms	9	10	4	3
Total metastatic neoplasms	14	23	7	3

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	456	517	536	565	573	609	620	662	676	729	729	729	729
Carcass ID Number	017	023	022	005	024	038	039	035	033	001	003	004	007
Alimentary System													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	M	+	+	+	+	+	M	+	+	+	+	+
Adenoma													
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous													
Intestine small, duodenum	A	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	+	+	+	+	+	+	+	+	+	+
Carcinoma						X							
Intestine small, ileum	A	A	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X		X					
Hepatocellular carcinoma				X	X	X	X						
Hepatocellular carcinoma, multiple								X					
Hepatocellular adenoma								X					
Hepatocellular adenoma, multiple	X												X
Hepatocholangiocarcinoma													
Mesentery			+					+					
Oral mucosa				+									
Pharyngeal, squamous cell carcinoma				X									
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma													
Stomach, glandular	A	A	+	+	+	+	+	+	+	+	+	+	+
Tooth		+	+	+	+			+	+	+	+	+	+
Cardiovascular System													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X					
Histiocytic sarcoma													
Endocrine System													
Adrenal cortex	A	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma													
Adrenal medulla	A	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign													
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													
Parathyroid gland	+	+	+	+	M	M	M	M	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	011	013	020	025	026	027	030	031	034	037	040	041
Alimentary System												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	M	+	+	+	+	+	+
Adenoma												
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous												
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X			
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X					
Hepatocellular carcinoma										X		
Hepatocellular carcinoma, multiple												
Hepatocellular adenoma			X		X							
Hepatocellular adenoma, multiple						X			X	X	X	
Hepatocholangiocarcinoma												
Mesentery	+					+	+					
Oral mucosa												
Pharyngeal, squamous cell carcinoma												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma												
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+		+	+	+	+	+	+		+	+
Cardiovascular System												
Heart	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma	X											
Histiocytic sarcoma												
Endocrine System												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma			X				X					
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign							X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												
Parathyroid gland	+	+	+	M	M	+	+	+	+	+	+	+
Pituitary gland	+	I	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	
Carcass ID Number	044	048	049	050	002	009	010	012	014	015	018	019	028	029	032	036	042	043	045	047	006	008	016	021	046	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	I	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	42
Adenoma		X																								1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous											X															1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma								X																		3
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										3
Hepatocellular carcinoma	X			X				X						X	X	X						X				12
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma														X		X	X	X	X		X			X		10
Hepatocellular adenoma, multiple		X	X				X			X										X		X				12
Hepatocholangiocarcinoma						X																				1
Mesentery		+				+									+				+		+			+		11
Oral mucosa																										1
Pharyngeal, squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma								X																		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth	+	+			+	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Histiocytic sarcoma						X																				1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma																		X								3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign				X																						2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma									X																	1
Parathyroid gland	+	+	M	+	+	+	+	M	+	+	M	+	M	M	+	+	+	+	+	M	+	+	+	M	M	35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

	4	5	5	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	5	1	3	6	7	0	2	6	7	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	6	7	6	5	3	9	0	2	6	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	1	2	2	0	2	3	3	3	3	0	0	0	0	1	1	2	2	2	2	3	3	3	3	4	4
	7	3	2	5	4	8	9	5	3	1	3	4	7	1	3	0	5	6	7	0	1	4	7	0	1
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									X
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Mast cell tumor malignant									X																
Lymph node, bronchial	+	+	M	M	+	M	M	+	+	+	+	+	M	M	M	M	+	M	+	+	+	M	+	+	+
Histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	M	+	+	+	+	+	+	+
Lymph node, mesenteric	A	+	+	+	+	I	+	+	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Lymph node, mediastinal	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	M	M	+
Histiocytic sarcoma																									
Mast cell tumor malignant, metastatic, bone marrow									X																
Sarcoma, metastatic, skin			X																						
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Mast cell tumor malignant, metastatic, bone marrow									X																
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrous histiocytoma																									
Subcutaneous tissue, sarcoma			X																						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	9	9	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total
Carcass ID Number	4	4	4	5	0	0	1	1	1	1	1	1	2	2	3	3	4	4	4	4	0	0	1	2	4	Tissues/
	4	8	9	0	2	9	0	2	4	5	8	9	8	9	2	6	2	3	5	7	6	8	6	1	6	Tumors
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																									X	1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																						X				2
Mast cell tumor malignant																										1
Lymph node, bronchial	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	35
Histiocytic sarcoma						X																				1
Lymph node, mandibular	+	M	M	+	+	+	I	+	+	+	+	M	+	M	+	+	+	M	M	+	+	+	+	+	+	39
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	44
Hemangiosarcoma																										1
Lymph node, mediastinal	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	M	+	+	+	+	37
Histiocytic sarcoma						X																				1
Mast cell tumor malignant, metastatic, bone marrow																										1
Sarcoma, metastatic, skin																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Mast cell tumor malignant, metastatic, bone marrow																										1
Thymus	+	+	M	+	+	+	M	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrous histiocytoma														X						X						2
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	456	517	536	565	573	609	620	662	676	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	017	023	022	005	024	038	039	035	033	001	003	004	007	011	013	020	025	026	027	030	031	034	037	040	041
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X								X			X		X					X				
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma													X					X					X		
Hemangiosarcoma, metastatic, liver						X																			
Hepatocellular carcinoma, metastatic, liver					X	X	X																		
Hepatocholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Mast cell tumor malignant, metastatic, bone marrow									X																
Sarcoma, metastatic, skin			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Renal tubule, carcinoma								X																	
Urinary bladder	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant																				X					

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	
Carcass ID Number	044	048	049	050	002	009	010	012	014	015	018	019	028	029	032	036	042	043	045	047	006	008	016	021	046	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma			X			X		X									X		X							10
Alveolar/bronchiolar adenoma, multiple											X		X													2
Alveolar/bronchiolar carcinoma			X				X																			5
Hemangiosarcoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver	X			X												X										6
Hepatocholangiocarcinoma, metastatic, liver						X																				1
Histiocytic sarcoma						X																				1
Mast cell tumor malignant, metastatic, bone marrow																										1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X					X							X	X										X		5
Carcinoma												X														1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver						X																				1
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Lymphoma malignant																										1

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 10 ppm

Number of Days on Study	338	543	556	600	629	639	641	672	697	702	711	716	729
Carcass ID Number	208	205	223	215	227	230	236	221	219	249	248	224	204
Alimentary System													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	I	+	A	+	+	M	+	A	+	A	I
Intestine large, colon	A	A	+	+	A	+	+	+	+	A	+	A	+
Intestine large, rectum	+	A	+	I	A	+	+	+	+	A	+	A	+
Leiomyosarcoma	X												
Intestine large, cecum	A	A	+	+	A	+	+	+	+	+	+	A	+
Carcinoma													
Hepatocholangiocarcinoma, metastatic, liver										X			
Intestine small, duodenum	A	A	+	+	A	+	+	+	+	A	+	A	+
Carcinoma							X						
Intestine small, jejunum	A	A	+	+	A	+	+	+	+	A	+	A	+
Intestine small, ileum	A	A	+	+	A	+	+	+	+	A	+	A	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma													
Hemangiosarcoma												X	
Hepatocellular carcinoma					X	X	X	X				X	
Hepatocellular carcinoma, multiple				X									
Hepatocellular adenoma		X								X			
Hepatocellular adenoma, multiple			X			X							
Hepatocholangiocarcinoma										X			
Mesentery													
Pancreas	A	A	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma													
Stomach, glandular	+	A	+	+	A	+	+	+	+	+	+	+	+
Tooth			+		+	+	+		+		+		+
Cardiovascular System													
Blood vessel											+		
Heart	+	A	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver													
Hepatocholangiocarcinoma, metastatic, liver										X			
Endocrine System													
Adrenal cortex	+	A	+	+	+	+	+	+	+	+	+	+	+
Adenoma													
Adrenal medulla	+	A	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	A	A	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	I	M	+	+	M	+	+	+	+	+	M	+	+
Pituitary gland	A	+	+	M	+	+	+	+	+	A	+	+	+
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma													
General Body System													
None													

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	210	212	213	214	228	233	235	238	242	243	244	245
Alimentary System												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	M	+	I	+	+	M	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma												
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma					X							
Hepatocholangiocarcinoma, metastatic, liver												
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma												
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma												
Hemangiosarcoma												
Hepatocellular carcinoma						X			X			X
Hepatocellular carcinoma, multiple												
Hepatocellular adenoma		X		X			X					X
Hepatocellular adenoma, multiple												
Hepatocholangiocarcinoma												
Mesentery			+			+						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma												
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+		+	+	+
Cardiovascular System												
Blood vessel												
Heart	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver												
Hepatocholangiocarcinoma, metastatic, liver												
Endocrine System												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma												
General Body System												
None												

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 10 ppm

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	Total
	4	0	0	0	0	0	1	1	2	2	2	3	3	3	0	1	1	2	2	3	3	4	4	4	5	Tissues/
	6	1	2	3	6	7	6	7	0	2	9	1	4	7	9	1	8	5	6	2	9	0	1	7	0	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	M	+	+	+	I	+	+	+	+	+	M	M	I	+	+	+	+	+	34
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leiomyosarcoma																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																									X	1
Hemangiosarcoma																										1
Hepatocellular carcinoma			X																							9
Hepatocellular carcinoma, multiple																			X							2
Hepatocellular adenoma		X		X							X						X					X	X			12
Hepatocellular adenoma, multiple								X					X		X											5
Hepatocholangiocarcinoma																										1
Mesentery							+											+								4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma											X															1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cholangiocarcinoma, metastatic, liver																									X	1
Hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																							X			1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma								X																		1
General Body System																										
None																										

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 10 ppm

Number of Days on Study	3	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	3	4	5	0	2	3	4	7	9	0	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2
	8	3	6	0	9	9	1	2	7	2	1	6	9	9	9	9	9	9	9	9	9	9	9	9	9
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	0	0	2	1	2	3	3	2	1	4	4	2	0	1	1	1	1	2	3	3	3	4	4	4	4
	8	5	3	5	7	0	6	1	9	9	8	4	4	0	2	3	4	8	3	5	8	2	3	4	5
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma															X										
Interstitial cell, adenoma													X												
Hematopoietic System																									
Bone marrow	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Lymph node	+									+															
Iliac, leiomyosarcoma, metastatic, intestine large, rectum	X																								
Pancreatic, hepatocholangiocarcinoma, metastatic, liver										X															
Lymph node, bronchial	A	+	M	M	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	M	+	M	+	+	M
Cholangiocarcinoma, metastatic, liver																									
Hepatocholangiocarcinoma, metastatic, liver										X															
Lymph node, mandibular	M	+	+	M	+	M	M	M	+	+	M	+	+	+	+	M	+	M	M	M	M	M	+	+	M
Lymph node, mesenteric	A	A	+	+	+	+	+	+	+	+	+	I	M	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver										X															
Lymph node, mediastinal	A	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	M	M	+
Carcinoma, metastatic, intestine small, duodenum							X																		
Cholangiocarcinoma, metastatic, liver																									
Hepatocholangiocarcinoma, metastatic, liver										X															
Spleen	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Thymus	A	M	M	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma																		X							
Subcutaneous tissue, sarcoma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+															
Cholangiocarcinoma, metastatic, liver																									
Hepatocholangiocarcinoma, metastatic, liver										X															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 10 ppm

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	246	201	202	203	206	207	216	217	220	222	229	231	234	237	209	211	218	225	226	232	239	240	241	247	250	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Interstitial cell, adenoma																						X				2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Lymph node																										2
Iliac, leiomyosarcoma, metastatic, intestine large, rectum																										1
Pancreatic, hepatocholangiocarcinoma, metastatic, liver																										1
Lymph node, bronchial	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	M	+	M	+	+	34
Cholangiocarcinoma, metastatic, liver																									X	1
Hepatocholangiocarcinoma, metastatic, liver																										1
Lymph node, mandibular	M	+	M	M	M	M	+	M	M	+	+	+	+	M	+	+	M	+	+	+	+	+	M	+	+	27
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hepatocholangiocarcinoma, metastatic, liver																										1
Lymph node, mediastinal	M	+	+	+	M	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	M	+	+	+	38
Carcinoma, metastatic, intestine small, duodenum																										1
Cholangiocarcinoma, metastatic, liver																									X	1
Hepatocholangiocarcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma												X														2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	41
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																									+	2
Cholangiocarcinoma, metastatic, liver																									X	1
Hepatocholangiocarcinoma, metastatic, liver																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 10 ppm

	3	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	4	5	0	2	3	4	7	9	0	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2
	8	3	6	0	9	9	1	2	7	2	1	6	9	9	9	9	9	9	9	9	9	9	9	9	9
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Carcass ID Number	0	0	2	1	2	3	3	2	1	4	4	2	0	1	1	1	1	2	3	3	3	4	4	4	4
	8	5	3	5	7	0	6	1	9	9	8	4	4	0	2	3	4	8	3	5	8	2	3	4	5
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X	X							
Alveolar/bronchiolar adenoma, multiple													X												
Alveolar/bronchiolar carcinoma											X														
Cholangiocarcinoma, metastatic, liver																									
Hemangiosarcoma, metastatic, liver												X													
Hepatocellular carcinoma, metastatic, liver								X				X										X			X
Hepatocholangiocarcinoma, metastatic, liver										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X		X												
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung											X														
Hepatocholangiocarcinoma, metastatic, liver										X															
Renal tubule, adenoma																									
Urinary bladder	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 10 ppm

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	246	201	202	203	206	207	216	217	220	222	229	231	234	237	209	211	218	225	226	232	239	240	241	247	250	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma	X										X											X				5
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma										X							X		X							4
Cholangiocarcinoma, metastatic, liver																									X	1
Hemangiosarcoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver																			X							5
Hepatocholangiocarcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X																									3
Carcinoma									X																	1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Renal tubule, adenoma									X																	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 30 ppm

	4	5	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	7	2	7	7	8	2	7	9	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3
	9	6	0	2	6	4	2	6	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	0
	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Carcass ID Number	1	0	4	4	0	4	1	3	2	2	2	2	3	3	3	3	3	4	4	0	0	0	1	1	2
	1	8	4	2	6	0	8	2	1	2	3	6	1	5	6	7	9	6	9	2	3	5	5	7	0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	M	I	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Intestine large, colon	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	I	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas	X																								
Hepatoblastoma	X						X																		
Hepatocellular carcinoma	X		X	X	X											X									
Hepatocellular carcinoma, multiple							X							X											
Hepatocellular adenoma						X				X													X		
Hepatocellular adenoma, multiple		X						X																	
Mesentery									+						+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X																								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Tooth						+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																	X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	M	M	+	I	+	+	+	+	+	M	+	+	+	+	+	+	M	M	M	M	+	M
Pituitary gland	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																								+	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 30 ppm

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	Total
	2	2	2	2	3	3	3	3	4	4	4	4	5	0	0	0	0	1	1	1	1	1	1	2	4	Tissues/
	4	5	8	9	0	3	4	8	1	3	5	7	0	1	4	7	9	0	2	3	4	6	9	7	8	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																										1
Hepatoblastoma																										2
Hepatocellular carcinoma			X					X																		7
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma			X	X							X		X		X				X				X			10
Hepatocellular adenoma, multiple																										2
Mesentery																	+						+			4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																					X					1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																			X							1
Tooth	+	+		+	+	+	+	+	+		+	+	+	+	+		+	+	+	+	+	+	+		+	41
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 30 ppm

Number of Days on Study	4	5	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	7	2	7	7	8	2	7	9	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3
	9	6	0	2	6	4	2	6	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	0
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	1	0	4	4	0	4	1	3	2	2	2	2	3	3	3	3	3	4	4	0	0	0	1	1	2
	1	8	4	2	6	0	8	2	1	2	3	6	1	5	6	7	9	6	9	2	3	5	5	7	0
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, bronchial	M	M	+	+	M	+	M	+	+	+	M	+	M	+	+	+	+	M	+	+	+	M	+	M	+
Lymph node, mandibular	+	M	+	+	+	M	M	+	+	M	+	+	+	+	+	M	M	M	+	M	+	+	+	+	M
Lymph node, mesenteric	+	A	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas	X																								
Lymph node, mediastinal	+	A	+	M	+	M	+	+	+	+	+	+	+	M	+	M	M	+	M	+	+	M	+	+	+
Carcinoma, metastatic, pancreas	X																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrous histiocytoma													X												
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																X									
Alveolar/bronchiolar carcinoma, multiple																									
Carcinoma, metastatic, pancreas	X																								
Hepatocellular carcinoma, metastatic, liver					X		X																		
Nose	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X								X				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																									

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 30 ppm

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	424	425	428	429	430	433	434	438	441	443	445	447	450	401	404	407	409	410	412	413	414	416	419	427	448	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+																							1
Lymph node, bronchial	+	+	+	+	+	M	+	+	+	M	+	+	M	+	M	+	M	M	M	+	+	+	M	+	+	33
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	M	+	M	+	M	M	+	+	+	+	+	+	M	+	+	+	35
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	47
Carcinoma, metastatic, pancreas																										1
Lymph node, mediastinal	M	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	M	M	M	+	M	M	+	+	+	33
Carcinoma, metastatic, pancreas																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	43
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrous histiocytoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma				X			X				X												X	X	X	6
Alveolar/bronchiolar carcinoma				X																						2
Alveolar/bronchiolar carcinoma, multiple												X														1
Carcinoma, metastatic, pancreas																										1
Hepatocellular carcinoma, metastatic, liver			X																							3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X	X			X									X					6
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant			X																							1

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	4	5	5	5	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	5	3	5	9	6	8	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	2	3	8	8	9	3	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Carcass ID Number	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	1	2	1	0	2	3	0	0	0	0	1	1	1	2	2	2	2	3	3	3	4	4	4	4	5
	9	4	1	3	7	0	1	2	5	9	3	7	8	0	1	5	9	2	4	6	3	4	5	7	0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	A	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma								X																	
Intestine small, duodenum	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma			X																						
Intestine small, ileum	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma											X														
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma		X							X			X													
Hepatocellular carcinoma, multiple																X		X							
Hepatocellular adenoma								X			X		X	X											X
Hepatocellular adenoma, multiple																								X	
Histiocytic sarcoma				X																					
Mesentery				+												+									+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma				X																					
Squamous cell papilloma																									
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth				+	+	+	+	+		+	+		+		+		+	+	+	+	+	+	+		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung					X																				
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	M	+	+
Pituitary gland	I	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	6 0 4	6 0 6	6 0 7	6 1 0	6 1 2	6 1 4	6 1 5	6 2 3	6 3 1	6 3 3	6 3 5	6 3 7	6 3 8	6 4 0	6 4 1	6 4 2	6 4 8	6 4 9	6 0 8	6 1 6	6 2 2	6 2 6	6 2 8	6 3 9	6 4 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	I	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma					X												X								X	4
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma												X	X		X		X									7
Hepatocellular carcinoma, multiple																							X			3
Hepatocellular adenoma		X	X				X		X									X	X							11
Hepatocellular adenoma, multiple																										1
Histiocytic sarcoma																										1
Mesentery						+																+				5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Squamous cell papilloma																				X						1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth		+	+	+	+	+	+		+	+	+			+	+	+	+	+		+	+	+		+	+	35
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	M	+	+	+	M	M	+	+	+	M	+	M	M	I	+	+	+	M	+	+	35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	452	533	558	598	669	683	719	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	619	624	611	603	627	630	601	602	605	609	613	617	618	620	621	625	629	632	634	636	643	644	645	647	650
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																					X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	M	+	+	M	M	+	+	M	+	+	M	+	+	+	M	+	M	+	M	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	M	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	M	+	+	+	+	M	M	M	M	+	+	+	+	+	+	M	+	M	+	M	M	M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach				X																					
Thymus	+	+	+	M	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X		X			X	X			X	X							X	X		X	
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma					X	X						X	X											X	
Alveolar/bronchiolar carcinoma, multiple																				X					
Fibroma																									
Hepatocellular carcinoma, metastatic, liver																X									
Bronchus, adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	604	606	607	610	612	614	615	623	631	633	635	637	638	640	641	642	648	649	608	616	622	626	628	639	646	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	M	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	37
Lymph node, mandibular	M	M	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	M	+	M	+	38
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	M	M	M	M	+	M	+	+	M	+	+	+	M	+	+	+	+	M	+	M	M	+	+	+	29
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Thymus	+	+	+	+	I	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma									X																	1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma											X						X				X		X			13
Alveolar/bronchiolar adenoma, multiple			X																			X				2
Alveolar/bronchiolar carcinoma														X		X	X									8
Alveolar/bronchiolar carcinoma, multiple																										1
Fibroma																								X		1
Hepatocellular carcinoma, metastatic, liver																										1
Bronchus, adenoma						X																				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	452	533	558	598	669	683	719	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	619	624	611	603	627	630	601	602	605	609	613	617	618	620	621	625	629	632	634	636	643	644	645	647	650
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X				X													X
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Lymphoma malignant																									

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	604	606	607	610	612	614	615	623	631	633	635	637	638	640	641	642	648	649	608	616	622	626	628	639	646	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X			X													X				X			7
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant								X																		1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Adrenal Cortex: Adenoma				
Overall rate[a]	3/49 (6%)	1/49 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rate[b]	6.6%	2.2%	0.0%	0.0%
Terminal rate[c]	3/41 (7%)	1/38 (3%)	0/42 (0%)	0/43 (0%)
First incidence (days)	729 (T)	729 (T)	—[e]	—
Poly-3 test[d]	P=0.104N	P=0.305N	P=0.115N	P=0.112N
Harderian Gland: Adenoma				
Overall rate	5/50 (10%)	3/50 (6%)	6/50 (12%)	7/50 (14%)
Adjusted rate	10.9%	6.5%	12.9%	14.8%
Terminal rate	5/41 (12%)	2/38 (5%)	6/42 (14%)	7/43 (16%)
First incidence (days)	729 (T)	711	729 (T)	729 (T)
Poly-3 test	P=0.221	P=0.353N	P=0.511	P=0.402
Harderian Gland: Adenoma or Carcinoma				
Overall rate	6/50 (12%)	4/50 (8%)	6/50 (12%)	7/50 (14%)
Adjusted rate	13.1%	8.7%	12.9%	14.8%
Terminal rate	6/41 (15%)	3/38 (8%)	6/42 (14%)	7/43 (16%)
First incidence (days)	729 (T)	711	729 (T)	729 (T)
Poly-3 test	P=0.347	P=0.365N	P=0.610N	P=0.525
Small Intestine (Jejunum): Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rate	6.5%	0.0%	0.0%	8.4%
Terminal rate	2/41 (5%)	0/38 (0%)	0/42 (0%)	3/43 (7%)
First incidence (days)	609	—	—	558
Poly-3 test	P=0.122	P=0.119N	P=0.118N	P=0.519
Small Intestine (Duodenum, Ileum, or Jejunum): Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	5/50 (10%)
Adjusted rate	6.5%	2.2%	0.0%	10.5%
Terminal rate	2/41 (5%)	0/38 (0%)	0/42 (0%)	4/43 (9%)
First incidence (days)	609	641	—	558
Poly-3 test	P=0.084	P=0.304N	P=0.118N	P=0.376
Liver: Hemangiosarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rate	6.5%	2.2%	0.0%	0.0%
Terminal rate	1/41 (2%)	0/38 (0%)	0/42 (0%)	0/43 (0%)
First incidence (days)	609	716	—	—
Poly-3 test	P=0.106N	P=0.308N	P=0.119N	P=0.116N
Liver: Hepatocellular Adenoma				
Overall rate	22/50 (44%)	17/50 (34%)	12/50 (24%)	12/50 (24%)
Adjusted rate	47.1%	35.8%	25.2%	25.4%
Terminal rate	20/41 (49%)	13/38 (34%)	9/42 (21%)	12/43 (28%)
First incidence (days)	456	543	526	729 (T)
Poly-3 test	P=0.039N	P=0.181N	P=0.020N	P=0.022N
Liver: Hepatocellular Carcinoma				
Overall rate	13/50 (26%)	11/50 (22%)	9/50 (18%)[f]	10/50 (20%)
Adjusted rate	27.2%	23.1%	18.4%	20.9%
Terminal rate	8/41 (20%)	5/38 (13%)	4/42 (10%)	9/43 (21%)
First incidence (days)	565	600	479	533
Poly-3 test	P=0.347N	P=0.411N	P=0.216N	P=0.317N

Table C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	30/50 (60%)	26/50 (52%)	20/50 (40%)[f]	22/50 (44%)
Adjusted rate	61.8%	53.2%	40.0%	46.0%
Terminal rate	24/41 (59%)	17/38 (45%)	12/42 (29%)	21/43 (49%)
First incidence (days)	456	543	479	533
Poly-3 test	P=0.131N	P=0.256N	P=0.023N	P=0.086N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	12/49 (24%)	6/49 (12%)	6/49 (12%)	15/49 (31%)
Adjusted rate	26.1%	13.2%	13.0%	31.6%
Terminal rate	11/41 (27%)	6/38 (16%)	6/42 (14%)	13/43 (30%)
First incidence (days)	536	729 (T)	729 (T)	598
Poly-3 test	P=0.067	P=0.097N	P=0.093N	P=0.358
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	5/49 (10%)	4/49 (8%)	3/49 (6%)	9/49 (18%)
Adjusted rate	11.0%	8.8%	6.5%	19.1%
Terminal rate	5/41 (12%)	3/38 (8%)	3/42 (7%)	7/43 (16%)
First incidence (days)	729 (T)	711	729 (T)	669
Poly-3 test	P=0.069	P=0.498N	P=0.349N	P=0.214
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	16/49 (33%)	10/49 (20%)	8/49 (16%)	20/49 (41%)
Adjusted rate	34.7%	21.9%	17.4%	42.0%
Terminal rate	15/41 (37%)	9/38 (24%)	8/42 (19%)	17/43 (40%)
First incidence (days)	536	711	729 (T)	598
Poly-3 test	P=0.053	P=0.128N	P=0.046N	P=0.306
Skin (Subcutaneous Tissue): Fibrous Histiocytoma or Sarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	6.5%	2.2%	2.2%	0.0%
Terminal rate	2/41 (5%)	0/38 (0%)	1/42 (2%)	0/43 (0%)
First incidence (days)	536	697	729 (T)	—
Poly-3 test	P=0.120N	P=0.307N	P=0.304N	P=0.115N
All Organs: Hemangiosarcoma				
Overall rate	6/50 (12%)	2/50 (4%)	0/50 (0%)	0/50 (0%)
Adjusted rate	12.9%	4.4%	0.0%	0.0%
Terminal rate	4/41 (10%)	1/38 (3%)	0/42 (0%)	0/43 (0%)
First incidence (days)	609	716	—	—
Poly-3 test	P=0.016N	P=0.136N	P=0.015N	P=0.014N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	6/50 (12%)	4/50 (8%)	0/50 (0%)	1/50 (2%)
Adjusted rate	12.9%	8.7%	0.0%	2.1%
Terminal rate	4/41 (10%)	3/38 (8%)	0/42 (0%)	1/43 (2%)
First incidence (days)	609	716	—	729 (T)
Poly-3 test	P=0.043N	P=0.375N	P=0.015N	P=0.053N
All Organs: Benign Neoplasms				
Overall rate	35/50 (70%)	24/50 (48%)	21/50 (42%)	27/50 (54%)
Adjusted rate	74.0%	50.4%	44.2%	56.5%
Terminal rate	32/41 (78%)	19/38 (50%)	18/42 (43%)	25/43 (58%)
First incidence (days)	456	543	526	598
Poly-3 test	P=0.279N	P=0.012N	P=0.002N	P=0.052N

Table C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
All Organs: Malignant Neoplasms				
Overall rate	26/50 (52%)	21/50 (42%)	14/50 (28%)	23/50 (46%)
Adjusted rate	53.5%	43.0%	28.7%	46.8%
Terminal rate	19/41 (46%)	11/38 (29%)	9/42 (21%)	18/43 (42%)
First incidence (days)	536	338	479	533
Poly-3 test	P=0.520N	P=0.202N	P=0.009N	P=0.322N
All Organs: Benign or Malignant Neoplasms				
Overall rate	43/50 (86%)	38/50 (76%)	29/50 (58%)	41/50 (82%)
Adjusted rate	87.1%	76.0%	58.0%	83.3%
Terminal rate	35/41 (85%)	26/38 (68%)	21/42 (50%)	36/43 (84%)
First incidence (days)	456	338	479	533
Poly-3 test	P=0.409	P=0.120N	P<0.001N	P=0.403N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, and lung; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Two animals with hepatocellular carcinoma also had hepatoblastoma.

TABLE C4
Historical Incidence of Alveolar/bronchiolar Neoplasms in Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence: Inhalation Studies			
Decalin	8/50	8/50	15/50
Divinylbenzene	12/49	5/49	16/49
Indium phosphide	13/50	6/50	18/50
Methyl isobutyl ketone	9/50	5/50	14/50
Propylene glycol mono-*t*-butyl ether	13/50	6/50	17/50
Stoddard solvent IIC	6/50	7/50	13/50
Vanadium pentoxide	13/50	12/50	22/50
Overall Historical Incidence: Inhalation Studies			
Total (%)	74/349 (21.2%)	49/349 (14.0%)	115/349 (33.0%)
Mean ± standard deviation	21.2% ± 5.8%	14.0% ± 4.9%	33.0% ± 6.0%
Range	12%-26%	10%-24%	26%-44%
Overall Historical Incidence: All Routes			
Total (%)	258/1,507 (17.1%)	151/1,507 (10.0%)	385/1,507 (25.6%)
Mean ± standard deviation	16.7% ± 7.3%	9.9% ± 5.0%	25.1% ± 9.4%
Range	4%-28%	4%-24%	12%-44%

[a] Data as of January 28, 2005

Table C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	10 ppm	30 ppm	100 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	7	6	5	4
Natural deaths	2	6	3	3
Survivors				
Terminal sacrifice	41	38	42	43
Animals examined microscopically	50	50	50	50
Alimentary System				
Liver	(50)	(50)	(50)	(50)
Angiectasis				1 (2%)
Basophilic focus	3 (6%)	6 (12%)	7 (14%)	4 (8%)
Clear cell focus	9 (18%)	11 (22%)	6 (12%)	5 (10%)
Eosinophilic focus	8 (16%)	7 (14%)		2 (4%)
Fatty change		2 (4%)	1 (2%)	
Infarct	2 (4%)		1 (2%)	
Inflammation, granulomatous	1 (2%)			
Mineralization	1 (2%)			
Mixed cell focus	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Necrosis	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Tension lipidosis	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Vacuolization cytoplasmic, focal	2 (4%)			
Mesentery	(11)	(4)	(4)	(5)
Fat, necrosis	10 (91%)	4 (100%)	4 (100%)	5 (100%)
Pancreas	(49)	(48)	(50)	(50)
Duct, cyst	2 (4%)			
Stomach, forestomach	(49)	(50)	(49)	(50)
Hyperplasia, squamous	1 (2%)	4 (8%)	2 (4%)	4 (8%)
Inflammation		1 (2%)		
Inflammation, acute		2 (4%)		1 (2%)
Inflammation, chronic active	1 (2%)	1 (2%)		3 (6%)
Mineralization				1 (2%)
Ulcer		2 (4%)	1 (2%)	1 (2%)
Stomach, glandular	(48)	(48)	(47)	(49)
Inflammation, acute		1 (2%)		
Mineralization		1 (2%)		
Necrosis		1 (2%)		1 (2%)
Tooth	(41)	(43)	(41)	(35)
Incisor, dysplasia	41 (100%)	43 (100%)	41 (100%)	35 (100%)
Cardiovascular System				
Heart	(50)	(49)	(50)	(50)
Cardiomyopathy	14 (28%)	5 (10%)	5 (10%)	5 (10%)
Mineralization	1 (2%)	1 (2%)		1 (2%)
Artery, inflammation, chronic active	1 (2%)			

[a] Number of animals examined microscopically at the site and the number of animals with lesion

Table C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Endocrine System				
Adrenal cortex	(49)	(49)	(50)	(50)
Hyperplasia	9 (18%)	10 (20%)	6 (12%)	5 (10%)
Hypertrophy	24 (49%)	25 (51%)	26 (52%)	24 (48%)
Adrenal medulla	(49)	(49)	(50)	(50)
Hyperplasia	1 (2%)	2 (4%)		2 (4%)
Parathyroid gland	(35)	(39)	(36)	(35)
Hyperplasia			1 (3%)	
Pituitary gland	(48)	(47)	(47)	(46)
Cyst		1 (2%)		
Pars distalis, hyperplasia	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Thyroid gland	(49)	(49)	(50)	(50)
Follicular cell, hyperplasia		2 (4%)	1 (2%)	
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	1 (2%)	2 (4%)		
Penis			(1)	
Inflammation, acute			1 (100%)	
Preputial gland	(50)	(50)	(50)	(50)
Ectasia	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Inflammation, chronic active			2 (4%)	
Seminal vesicle	(49)	(48)	(50)	(49)
Inflammation, chronic		1 (2%)		
Testes	(50)	(50)	(50)	(50)
Atrophy	2 (4%)			
Mineralization	1 (2%)			
Interstitial cell, hyperplasia			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(48)	(50)	(50)
Necrosis	1 (2%)			
Spleen	(49)	(48)	(50)	(50)
Hematopoietic cell proliferation	1 (2%)		1 (2%)	
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Inflammation, chronic active	3 (6%)	1 (2%)		2 (4%)
Inflammation, granulomatous				1 (2%)
Subcutaneous tissue, cyst epithelial inclusion		1 (2%)		
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Necrosis, focal	1 (2%)			
Artery, inflammation, chronic active	1 (2%)			

Table C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)			
Lung	(49)	(49)	(49)	(49)
Hemorrhage	1 (2%)			1 (2%)
Mineralization		1 (2%)		
Alveolar epithelium, hyperplasia	1 (2%)	5 (10%)	5 (10%)	7 (14%)
Alveolus, infiltration cellular, histiocyte	2 (4%)	4 (8%)	5 (10%)	1 (2%)
Bronchiole, hyperplasia			1 (2%)	
Bronchiole, hyperplasia, atypical		38 (78%)	46 (94%)	46 (94%)
Bronchiole, inflammation, chronic active				1 (2%)
Nose	(50)	(50)	(49)	(50)
Inflammation, suppurative	3 (6%)	47 (94%)	49 (100%)	49 (98%)
Glands, necrosis		1 (2%)		
Glands, respiratory epithelium, metaplasia	12 (24%)	50 (100%)	49 (100%)	50 (100%)
Olfactory epithelium, atrophy	14 (28%)			
Olfactory epithelium, degeneration, hyaline	5 (10%)	50 (100%)	48 (98%)	11 (22%)
Olfactory epithelium, respiratory epithelium, metaplasia	1 (2%)	50 (100%)	49 (100%)	50 (100%)
Respiratory epithelium, metaplasia, squamous				1 (2%)
Sinus, foreign body			1 (2%)	
Special Senses System				
Eye	(49)	(47)	(47)	(50)
Phthisis bulbi			1 (2%)	1 (2%)
Cornea, inflammation, chronic active		2 (4%)	1 (2%)	1 (2%)
Cornea, mineralization				2 (4%)
Harderian gland	(50)	(49)	(50)	(50)
Hyperplasia	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst	1 (2%)		2 (4%)	
Infarct	1 (2%)	2 (4%)	1 (2%)	
Inflammation, suppurative	1 (2%)			
Metaplasia, osseous	7 (14%)	3 (6%)	5 (10%)	1 (2%)
Nephropathy	45 (90%)	43 (86%)	40 (80%)	34 (68%)
Capsule, fibrosis	1 (2%)			
Papilla, necrosis	1 (2%)			
Pelvis, dilatation		1 (2%)		
Renal tubule, hyperplasia	2 (4%)	1 (2%)		
Renal tubule, necrosis				1 (2%)
Urinary bladder	(48)	(48)	(49)	(49)
Transitional epithelium, hyperplasia	1 (2%)			

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF DIVINYLBENZENE-HP

TABLE D1	Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP	D-2
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Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	10 ppm	30 ppm	100 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death			1	
Moribund	11	12	8	7
Natural deaths	6	3	3	1
Survivors				
Terminal sacrifice	33	35	38	42
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(45)	(41)	(36)	(41)
Intestine large, colon	(48)	(50)	(50)	(50)
Intestine large, cecum	(47)	(49)	(48)	(50)
Intestine small, duodenum	(46)	(48)	(48)	(49)
Carcinoma			1 (2%)	
Histiocytic sarcoma	1 (2%)			
Intestine small, jejunum	(46)	(48)	(48)	(49)
Carcinoma		2 (4%)		
Liver	(49)	(50)	(50)	(50)
Hepatocellular carcinoma	3 (6%)	4 (8%)	3 (6%)	2 (4%)
Hepatocellular carcinoma, multiple	2 (4%)			
Hepatocellular adenoma	12 (24%)	4 (8%)	5 (10%)	4 (8%)
Hepatocellular adenoma, multiple	5 (10%)	3 (6%)	1 (2%)	1 (2%)
Hepatocholangiocarcinoma	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Mesentery	(17)	(16)	(4)	(5)
Pancreas	(48)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(49)	(50)	(49)	(49)
Adenoma	1 (2%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Carcinoma, metastatic, mammary gland				1 (2%)
Sarcoma		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma	1 (2%)			
Adrenal medulla	(49)	(50)	(49)	(50)
Histiocytic sarcoma	1 (2%)			
Pheochromocytoma malignant				2 (4%)
Pheochromocytoma benign			1 (2%)	
Islets, pancreatic	(48)	(49)	(49)	(50)
Carcinoma	1 (2%)			
Pituitary gland	(47)	(50)	(49)	(45)
Histiocytic sarcoma	1 (2%)			
Pars distalis, adenoma	8 (17%)	8 (16%)	1 (2%)	1 (2%)
Pars intermedia, adenoma	1 (2%)			
Thyroid gland	(49)	(49)	(50)	(48)

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
General Body System				
None				
Genital System				
Ovary	(48)	(50)	(49)	(49)
Cystadenoma	3 (6%)			1 (2%)
Hemangioma				1 (2%)
Histiocytic sarcoma	1 (2%)			
Luteoma	1 (2%)			
Uterus	(49)	(50)	(50)	(49)
Adenoma				1 (2%)
Carcinoma				1 (2%)
Fibroma		1 (2%)		
Histiocytic sarcoma			2 (4%)	
Polyp stromal	1 (2%)	3 (6%)		2 (4%)
Hematopoietic System				
Bone marrow	(49)	(49)	(50)	(50)
Hemangiosarcoma		2 (4%)		
Histiocytic sarcoma	1 (2%)			
Sarcoma, metastatic, skin			1 (2%)	
Lymph node	(9)	(3)	(5)	(2)
Renal, carcinoma, metastatic, mammary gland				1 (50%)
Lymph node, bronchial	(43)	(46)	(39)	(39)
Lymph node, mandibular	(41)	(45)	(44)	(41)
Histiocytic sarcoma	1 (2%)			
Lymph node, mesenteric	(49)	(50)	(49)	(49)
Carcinoma, metastatic, mammary gland				1 (2%)
Histiocytic sarcoma	1 (2%)			
Lymph node, mediastinal	(44)	(44)	(38)	(38)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (3%)
Carcinoma, metastatic, mammary gland				1 (3%)
Hepatocholangiocarcinoma, metastatic, liver				1 (3%)
Histiocytic sarcoma	1 (2%)			
Spleen	(49)	(50)	(49)	(49)
Hemangiosarcoma		3 (6%)		
Histiocytic sarcoma	1 (2%)			
Thymus	(49)	(47)	(46)	(44)
Carcinoma, metastatic, mammary gland				1 (2%)
Histiocytic sarcoma	1 (2%)			
Integumentary System				
Mammary gland	(50)	(49)	(50)	(49)
Carcinoma		2 (4%)		
Carcinoma, multiple				1 (2%)
Skin	(50)	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)			
Subcutaneous tissue, hemangiosarcoma	1 (2%)	1 (2%)		
Subcutaneous tissue, neural crest tumor	1 (2%)			
Subcutaneous tissue, sarcoma	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Subcutaneous tissue, sarcoma, multiple		1 (2%)	1 (2%)	

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteoma		1 (2%)		
Osteosarcoma			1 (2%)	
Skeletal muscle		(1)		(1)
Carcinoma, metastatic, mammary gland				1 (100%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Meningioma benign			1 (2%)	
Respiratory System				
Larynx	(48)	(50)	(50)	(49)
Lung	(50)	(50)	(50)	(49)
Alveolar/bronchiolar adenoma	4 (8%)	9 (18%)	4 (8%)	6 (12%)
Alveolar/bronchiolar adenoma, multiple				2 (4%)
Alveolar/bronchiolar carcinoma	2 (4%)	3 (6%)	4 (8%)	5 (10%)
Alveolar/bronchiolar carcinoma, multiple		2 (4%)		
Carcinoma, metastatic, mammary gland				1 (2%)
Hemangiosarcoma, metastatic, spleen		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	3 (6%)	2 (4%)		1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Sarcoma, metastatic, skin		2 (4%)	1 (2%)	
Nose	(50)	(50)	(50)	(49)
Hemangioma	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Olfactory epithelium, neuroblastoma				1 (2%)
Trachea	(49)	(50)	(50)	(50)
Special Senses System				
Eye	(50)	(50)	(50)	(49)
Harderian gland	(50)	(50)	(50)	(50)
Adenoma	4 (8%)	1 (2%)	4 (8%)	5 (10%)
Carcinoma	2 (4%)	4 (8%)	1 (2%)	2 (4%)
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Carcinoma, metastatic, mammary gland				1 (2%)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma	1 (2%)			
Renal tubule, adenoma				1 (2%)
Urinary bladder	(49)	(50)	(50)	(49)
Systemic Lesions				
Multiple organs[c]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		2 (4%)	
Lymphoma malignant	11 (22%)	10 (20%)	5 (10%)	1 (2%)

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	40	40	26	26
Total primary neoplasms	68	66	37	41
Total animals with benign neoplasms	28	21	14	19
Total benign neoplasms	42	30	17	25
Total animals with malignant neoplasms	22	29	19	13
Total malignant neoplasms	25	36	20	16
Total animals with metastatic neoplasms	4	5	2	2
Total metastatic neoplasms	4	6	2	12
Total animals with uncertain neoplasms—benign or malignant	1			
Total uncertain neoplasms	1			

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm.
[b] Number of animals with any tissue examined microscopically.
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	352	366	386	450	479	576	586	596	625	658	660	676	681	687	709	710	711	731	731	731	731	731	731	731	732
Carcass ID Number	109	140	116	124	148	101	117	105	134	123	138	103	118	147	133	121	127	113	119	122	125	139	142	145	102
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	A	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	A	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma							X		X																
Hepatocellular carcinoma, multiple																			X	X					
Hepatocellular adenoma													X				X		X			X	X		
Hepatocellular adenoma, multiple									X	X										X					
Hepatocholangiocarcinoma															X										
Histiocytic sarcoma					X																				
Mesentery							+		+					+	+	+			+	+			+		
Pancreas	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Tooth													+						+						
Cardiovascular System																									
Blood vessel			+																						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																X									
Parathyroid gland	+	M	+	M	M	+	+	+	+	+	+	M	M	M	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Pars distalis, adenoma								X							X										X
Pars intermedia, adenoma																						X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

+: Tissue examined microscopically M: Missing tissue X: Lesion present
A: Autolysis precludes examination I: Insufficient tissue Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	104	106	110	111	114	115	128	130	137	141	143	150	107	108	112	120	126	129	131	132	135	136	144	146	149	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma											X															3
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma					X			X	X	X				X				X			X					12
Hepatocellular adenoma, multiple		X		X																						5
Hepatocholangiocarcinoma																										1
Histiocytic sarcoma																										1
Mesentery				+			+			+						+		+		+		+		+	+	17
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma															X											1
Tooth	+	+		+								+					+					+		+		9
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	49
Histiocytic sarcoma																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																										1
Parathyroid gland	+	I	+	+	+	+	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	36
Pituitary gland	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	47
Histiocytic sarcoma																										1
Pars distalis, adenoma	X			X				X					X				X									8
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
None																										

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	352	366	386	450	479	576	586	596	625	658	660	676	681	687	709	710	711	731	731	731	731	731	731	731	732
Carcass ID Number	109	140	116	124	148	101	117	105	134	123	138	103	118	147	133	121	127	113	119	122	125	139	142	145	102
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	I	+	+	+	+	+	+	+	+
Cystadenoma																								X	
Histiocytic sarcoma					X																				
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Lymph node			+							+		+	+			+					+		+	+	
Lymph node, bronchial	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+
Histiocytic sarcoma					X																				
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	M
Histiocytic sarcoma					X																				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, hemangiosarcoma																	X								
Subcutaneous tissue, neural crest tumor																									
Subcutaneous tissue, sarcoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: control

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	104	106	110	111	114	115	128	130	137	141	143	150	107	108	112	120	126	129	131	132	135	136	144	146	149	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma															X					X						3
Histiocytic sarcoma																										1
Luteoma																					X					1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal																					X					1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node														+												9
Lymph node, bronchial	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	43
Lymph node, mandibular	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	41
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node, mediastinal	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	44
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma					X																					1
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, neural crest tumor									X																	1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	352	366	386	450	479	576	586	596	625	658	660	676	681	687	709	710	711	731	731	731	731	731	731	731	732
Carcass ID Number	109	140	116	124	148	101	117	105	134	123	138	103	118	147	133	121	127	113	119	122	125	139	142	145	102
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver									X										X						
Hepatocholangiocarcinoma, metastatic, liver															X										
Histiocytic sarcoma					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma															X										
Histiocytic sarcoma					X																				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X							X										
Carcinoma														X						X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Lymphoma malignant			X				X			X		X	X			X		X							

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: Chamber Control

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	104	106	110	111	114	115	128	130	137	141	143	150	107	108	112	120	126	129	131	132	135	136	144	146	149	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X					X	X																		4
Alveolar/bronchiolar carcinoma					X											X										2
Hepatocellular carcinoma, metastatic, liver											X															3
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Histiocytic sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																	X						4
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant							X														X	X			X	11

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 10 ppm

Number of Days on Study	506	515	537	550	564	586	613	638	656	693	707	709	715	719	725	731	731	731	731	731	731	731	731	732	732
Carcass ID Number	318	350	323	312	305	321	342	308	307	314	348	337	319	343	326	304	306	320	322	329	333	340	341	302	310
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	I	M	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	I	+	+	+	M	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma														X						X					
Hepatocellular adenoma			X														X								X
Hepatocellular adenoma, multiple															X										
Mesentery		+		+	+			+				+		+	+				+						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth				+						+	+										+	+			
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma		X																							
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																				X					
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	M	+	+	+	M	+	+	M	+	+	+	I	M	+	+	M	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X	X													X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	M	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																X									
Polyp stromal																				X					

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 10 ppm

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Total
	1	1	1	2	2	2	2	3	3	3	3	3	3	4	4	4	0	0	0	1	1	3	3	4	4	Tissues/
	5	6	7	4	5	7	8	0	1	2	5	8	9	4	6	7	1	3	9	1	3	4	6	5	9	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma									X																X	2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma									X															X		4
Hepatocellular adenoma																				X						4
Hepatocellular adenoma, multiple									X										X							3
Mesentery	+		+	+			+	+									+		+						+	16
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth		+					+			+		+	+		+							+	+			13
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	M	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X									X								X				X	8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	M	+	+	M	+	I	+	M	+	+	+	+	+	M	+	+	41
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																										1
Polyp stromal									X											X						3

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 10 ppm

Number of Days on Study	506	515	537	550	564	586	613	638	656	693	707	709	715	719	725	731	731	731	731	731	731	731	731	732	732
Carcass ID Number	318	350	323	312	305	321	342	308	307	314	348	337	319	343	326	304	306	320	322	329	333	340	341	302	310
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X																
Lymph node					+	+							+												
Lymph node, bronchial	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X																
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma							X										X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma									X																
Subcutaneous tissue, sarcoma								X																	
Subcutaneous tissue, sarcoma, multiple	X																								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteoma			X																						
Skeletal muscle				+																					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X								X	
Alveolar/bronchiolar carcinoma														X											
Alveolar/bronchiolar carcinoma, multiple																									
Hemangiosarcoma, metastatic, spleen									X																
Hepatocellular carcinoma, metastatic, liver																				X					
Sarcoma, metastatic, skin	X							X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																								X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 10 ppm

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Total
Carcass ID Number	1	1	1	2	2	2	2	3	3	3	3	3	3	4	4	4	0	0	0	1	1	3	3	4	4	Tissues/
	5	6	7	4	5	7	8	0	1	2	5	8	9	4	6	7	1	3	9	1	3	4	6	5	9	Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma			X																							2
Lymph node																										3
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	M	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X																		X					3
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, sarcoma																										1
Subcutaneous tissue, sarcoma, multiple																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteoma																										1
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X		X	X								X	X	X						X						9
Alveolar/bronchiolar carcinoma														X									X			3
Alveolar/bronchiolar carcinoma, multiple								X												X						2
Hemangiosarcoma, metastatic, spleen																										1
Hepatocellular carcinoma, metastatic, liver									X																	2
Sarcoma, metastatic, skin																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																			1
Carcinoma									X						X		X									4

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 10 ppm

Number of Days on Study	506	515	537	550	564	586	613	638	656	693	707	709	715	719	725	731	731	731	731	731	731	731	731	732	732
Carcass ID Number	318	350	323	312	305	321	342	308	307	314	348	337	319	343	326	304	306	320	322	329	333	340	341	302	310
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant				X	X	X						X	X									X			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 10 ppm

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Total
Carcass ID Number	1	1	1	2	2	2	2	3	3	3	3	3	3	4	4	4	0	0	0	1	1	3	3	4	4	Tissues/
	5	6	7	4	5	7	8	0	1	2	5	8	9	4	6	7	1	3	9	1	3	4	6	5	9	Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant	X					X									X							X				10

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 30 ppm

Number of Days on Study	334	359	501	512	536	550	564	577	600	709	711	719	731	731	731	731	731	731	731	732	732	732	732	732	732
Carcass ID Number	517	519	537	542	529	531	524	514	522	511	527	548	506	521	523	530	535	536	541	502	507	512	518	528	533
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	A	+	I	+	+	A	+	+	+	+	+	+	+	+	I	I	I	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, jejunum	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma			X																						
Hepatocellular adenoma										X															
Hepatocellular adenoma, multiple																									
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth															+		+			+				+	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	+	+	+	M	+	+	M	+	+	+	M	M	M	M	M	+	+	+	M	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma															X										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	M	M	M	+	I	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 30 ppm

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	5 3 8	5 3 9	5 4 0	5 4 5	5 4 6	5 4 9	5 5 0	5 0 1	5 0 3	5 0 4	5 0 5	5 0 8	5 0 9	5 1 0	5 1 3	5 1 5	5 1 6	5 2 0	5 2 5	5 2 6	5 3 2	5 3 4	5 4 3	5 4 4	5 4 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	M	+	I	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	I	I	M	36
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma										X																1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X																								X	3
Hepatocellular adenoma					X				X								X								X	5
Hepatocellular adenoma, multiple										X																1
Mesentery		+								+							+					+				4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth							+							+		+				+						8
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	M	+	+	35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	44
Ovary	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma															X											2

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 30 ppm

Number of Days on Study	334	359	501	512	536	550	564	577	600	709	711	719	731	731	731	731	731	731	731	732	732	732	732	732	732
Carcass ID Number	517	519	537	542	529	531	524	514	522	511	527	548	506	521	523	530	535	536	541	502	507	512	518	528	533
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin																									
Lymph node						+				+		+													+
Lymph node, bronchial	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	M
Spleen	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma							X																		
Subcutaneous tissue, sarcoma, multiple											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																								X	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma benign																									X
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X															
Alveolar/bronchiolar carcinoma					X																				
Sarcoma, metastatic, skin											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Lymphoma malignant						X				X		X			X										

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 30 ppm

Number of Days on Study	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	538	539	540	545	546	549	550	501	503	504	505	508	509	510	513	515	516	520	525	526	532	534	543	544	547	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, skin			X																							1
Lymph node																				+						5
Lymph node, bronchial	+	M	M	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	39
Lymph node, mandibular	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	M	M	+	+	+	M	M	+	+	+	+	+	+	+	+	M	M	+	+	M	+	38
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma			X																							2
Subcutaneous tissue, sarcoma, multiple																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma benign																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X								X												X				4
Alveolar/bronchiolar carcinoma									X								X						X			4
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X	X			X							4
Carcinoma																				X						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma															X											2
Lymphoma malignant																				X						5

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	200	383	407	697	697	704	725	729	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732
Carcass ID Number	746	709	743	703	744	747	712	713	704	705	710	711	722	738	745	701	706	707	715	716	718	726	727	728	730
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	I	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	I
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																X									
Hepatocellular adenoma																							X	X	
Hepatocellular adenoma, multiple																									
Mesentery					+																	+		+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth							+					+	+				+			+	+		+	+	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland								X																	
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant										X														X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	M	+	+	+	+	+	M	M	+	+	+	M	M	+	+	M	+	+	+
Pituitary gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pars distalis, adenoma									X																
Thyroid gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Hemangioma																									
Uterus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Polyp stromal																									

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	Total
Carcass ID Number	3	3	3	4	4	4	0	0	1	1	1	2	2	2	2	2	2	3	3	3	3	3	4	4	5	Tissues/
	1	2	5	2	8	9	2	8	4	7	9	0	1	3	4	5	9	3	4	6	7	9	0	1	0	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	I	+	I	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma															X											2
Hepatocellular adenoma										X											X					4
Hepatocellular adenoma, multiple																		X								1
Mesentery																+		+								5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth						+	+							+	+		+							+	+	15
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	39
Pituitary gland	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	45
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
General Body System																										
None																										
Genital System																										
Clitoral gland	I	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma															X											1
Hemangioma										X																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																	X									1
Carcinoma												X														1
Polyp stromal										X													X			2

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	200	383	407	697	697	704	725	729	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732
Carcass ID Number	746	709	743	703	744	747	712	713	704	705	710	711	722	738	745	701	706	707	715	716	718	726	727	728	730
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+		+																	
Renal, carcinoma, metastatic, mammary gland								X																	
Lymph node, bronchial	+	+	M	+	M	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland								X																	
Lymph node, mediastinal	+	M	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Carcinoma, metastatic, mammary gland								X																	
Hepatocholangiocarcinoma, metastatic, liver																									
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	M	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland								X																	
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, multiple								X																	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle								+																	
Carcinoma, metastatic, mammary gland								X																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X										X											
Alveolar/bronchiolar adenoma, multiple										X															
Alveolar/bronchiolar carcinoma								X					X												
Carcinoma, metastatic, mammary gland								X																	
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Olfactory epithelium, neuroblastoma																							X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	731	732	735	742	748	749	702	708	714	717	719	720	721	723	724	725	729	733	734	736	737	739	740	741	750	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										2
Renal, carcinoma, metastatic, mammary gland																										1
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	M	+	+	+	+	39
Lymph node, mandibular	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	41
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, mammary gland																										1
Lymph node, mediastinal	+	+	M	+	+	M	M	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	38
Alveolar/bronchiolar carcinoma, metastatic, lung															X											1
Carcinoma, metastatic, mammary gland																										1
Hepatocholangiocarcinoma, metastatic, liver															X											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma, metastatic, mammary gland																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Carcinoma, metastatic, mammary gland																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma					X					X												X			X	6
Alveolar/bronchiolar adenoma, multiple	X																									2
Alveolar/bronchiolar carcinoma								X							X			X								5
Carcinoma, metastatic, mammary gland																										1
Hepatocellular carcinoma, metastatic, liver															X											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Olfactory epithelium, neuroblastoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	203	383	407	697	697	704	725	729	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732
Carcass ID Number	746	709	743	703	744	747	712	713	704	705	710	711	722	738	745	701	706	707	715	716	718	726	727	728	730
Special Senses System																									
Eye	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Carcinoma											X								X						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland								X																	
Hepatocellular carcinoma, metastatic, liver																									
Renal tubule, adenoma														X											
Urinary bladder	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																									

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP: 100 ppm

Number of Days on Study	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	731	732	735	742	748	749	702	708	714	717	719	720	721	723	724	725	729	733	734	736	737	739	740	741	750	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X		X	X																	X					5
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																										1
Hepatocellular carcinoma, metastatic, liver															X											1
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant											X															1

Table D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Harderian Gland: Adenoma				
Overall rate[a]	4/50 (8%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted rate[b]	9.3%	2.2%	9.1%	10.7%
Terminal rate[c]	2/33 (6%)	1/35 (3%)	4/38 (11%)	4/42 (10%)
First incidence (days)	596	731 (T)	731 (T)	725
Poly-3 test[d]	P=0.258	P=0.167N	P=0.634N	P=0.551
Harderian Gland: Carcinoma				
Overall rate	2/50 (4%)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted rate	4.7%	8.9%	2.3%	4.3%
Terminal rate	1/33 (3%)	4/35 (11%)	1/38 (3%)	2/42 (5%)
First incidence (days)	687	731 (T)	731 (T)	731 (T)
Poly-3 test	P=0.430N	P=0.359	P=0.491N	P=0.661N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	6/50 (12%)	5/50 (10%)	5/50 (10%)	7/50 (14%)
Adjusted rate	13.8%	11.1%	11.4%	14.9%
Terminal rate	3/33 (9%)	5/35 (14%)	5/38 (13%)	6/42 (14%)
First incidence (days)	596	731 (T)	731 (T)	725
Poly-3 test	P=0.417	P=0.475N	P=0.491N	P=0.560
Liver: Hepatocellular Adenoma				
Overall rate	17/49 (35%)	7/50 (14%)	6/50 (12%)	5/50 (10%)
Adjusted rate	39.7%	15.4%	13.6%	10.7%
Terminal rate	13/33 (39%)	5/35 (14%)	5/38 (13%)	5/42 (12%)
First incidence (days)	625	537	709	731 (T)
Poly-3 test	P=0.010N	P=0.008N	P=0.004N	P<0.001N
Liver: Hepatocellular Carcinoma				
Overall rate	5/49 (10%)	4/50 (8%)	3/50 (6%)	2/50 (4%)
Adjusted rate	11.7%	8.9%	6.7%	4.3%
Terminal rate	3/33 (9%)	3/35 (9%)	2/38 (5%)	2/42 (5%)
First incidence (days)	586	719	501	731 (T)
Poly-3 test	P=0.162N	P=0.467N	P=0.332N	P=0.180N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	19/49 (39%)	10/50 (20%)	8/50 (16%)	7/50 (14%)
Adjusted rate	43.9%	21.9%	17.9%	14.9%
Terminal rate	14/33 (42%)	7/35 (20%)	6/38 (16%)	7/42 (17%)
First incidence (days)	586	537	501	731 (T)
Poly-3 test	P=0.012N	P=0.021N	P=0.006N	P=0.002N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	4/50 (8%)	9/50 (18%)	4/50 (8%)	8/49 (16%)
Adjusted rate	9.4%	20.0%	9.1%	17.1%
Terminal rate	4/33 (12%)	9/35 (26%)	3/38 (8%)	7/42 (17%)
First incidence (days)	731 (T)	731 (T)	709	697
Poly-3 test	P=0.352	P=0.134	P=0.626N	P=0.225
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	5/50 (10%)	4/50 (8%)	5/49 (10%)
Adjusted rate	4.7%	11.1%	9.0%	10.7%
Terminal rate	2/33 (6%)	4/35 (11%)	3/38 (8%)	4/42 (10%)
First incidence (days)	731 (T)	719	536	729
Poly-3 test	P=0.360	P=0.238	P=0.357	P=0.255

Table D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	6/50 (12%)	12/50 (24%)	8/50 (16%)	13/49 (27%)
Adjusted rate	14.1%	26.7%	17.9%	27.7%
Terminal rate	6/33 (18%)	11/35 (31%)	6/38 (16%)	11/42 (26%)
First incidence (days)	731 (T)	719	536	697
Poly-3 test	P=0.161	P=0.114	P=0.421	P=0.092
Ovary: Cystadenoma				
Overall rate	3/48 (6%)	0/50 (0%)	0/49 (0%)	1/49 (2%)
Adjusted rate	7.3%	0.0%	0.0%	2.2%
Terminal rate	3/33 (9%)	0/35 (0%)	0/37 (0%)	1/41 (2%)
First incidence (days)	731 (T)	—[e]	—	731 (T)
Poly-3 test	P=0.475N	P=0.102N	P=0.110N	P=0.265N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	8/47 (17%)	8/50 (16%)	1/49 (2%)	1/45 (2%)
Adjusted rate	19.8%	17.7%	2.3%	2.3%
Terminal rate	6/31 (19%)	6/35 (17%)	1/37 (3%)	1/38 (3%)
First incidence (days)	596	693	731 (T)	731 (T)
Poly-3 test	P=0.005N	P=0.511N	P=0.011N	P=0.012N
Skin (Subcutaneous): Sarcoma				
Overall rate	1/50 (2%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rate	2.3%	4.4%	6.7%	2.1%
Terminal rate	0/33 (0%)	0/35 (0%)	1/38 (3%)	0/42 (0%)
First incidence (days)	450	506	564	697
Poly-3 test	P=0.469N	P=0.520	P=0.314	P=0.743N
Spleen: Hemangiosarcoma				
Overall rate	0/49 (0%)	3/50 (6%)	0/49 (0%)	0/49 (0%)
Adjusted rate	0.0%	6.6%	0.0%	0.0%
Terminal rate	0/33 (0%)	2/35 (6%)	0/38 (0%)	0/42 (0%)
First incidence (days)	—	656	—	—
Poly-3 test	P=0.246N	P=0.133	—[f]	—
Uterus: Stromal Polyp				
Overall rate	1/50 (2%)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted rate	2.3%	6.7%	0.0%	4.3%
Terminal rate	1/33 (3%)	3/35 (9%)	0/38 (0%)	2/42 (5%)
First incidence (days)	731 (T)	731 (T)	—	731 (T)
Poly-3 test	P=0.596	P=0.324	P=0.494N	P=0.533
All Organs: Hemangiosarcoma				
Overall rate	1/50 (2%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	2.3%	6.6%	0.0%	0.0%
Terminal rate	0/33 (0%)	2/35 (6%)	0/38 (0%)	0/42 (0%)
First incidence (days)	711	656	—	—
Poly-3 test	P=0.149N	P=0.326	P=0.495N	P=0.482N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	4.7%	6.6%	0.0%	2.1%
Terminal rate	0/33 (0%)	2/35 (6%)	0/38 (0%)	1/42 (2%)
First incidence (days)	709	656	—	731 (T)
Poly-3 test	P=0.296N	P=0.525	P=0.231N	P=0.469N

Table D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
All Organs: Malignant Lymphoma				
Overall rate	11/50 (22%)	10/50 (20%)	5/50 (10%)	1/50 (2%)
Adjusted rate	24.6%	21.4%	11.2%	2.1%
Terminal rate	5/33 (15%)	5/35 (14%)	2/38 (5%)	1/42 (2%)
First incidence (days)	386	550	550	731 (T)
Poly-3 test	P<0.001N	P=0.456N	P=0.083N	P<0.001N
All Organs: Benign Neoplasms				
Overall rate	28/50 (56%)	21/50 (42%)	14/50 (28%)	19/50 (38%)
Adjusted rate	63.4%	45.8%	31.8%	40.4%
Terminal rate	22/33 (67%)	17/35 (49%)	13/38 (34%)	17/42 (41%)
First incidence (days)	596	537	709	697
Poly-3 test	P=0.077N	P=0.066N	P=0.002N	P=0.020N
All Organs: Malignant Neoplasms				
Overall rate	22/50 (44%)	29/50 (58%)	19/50 (38%)	13/50 (26%)
Adjusted rate	46.8%	59.0%	40.8%	27.6%
Terminal rate	10/33 (30%)	18/35 (51%)	12/38 (32%)	11/42 (26%)
First incidence (days)	386	506	501	697
Poly-3 test	P=0.004N	P=0.158	P=0.352N	P=0.041N
All Organs: Benign or Malignant Neoplasms				
Overall rate	40/50 (80%)	40/50 (80%)	26/50 (52%)	26/50 (52%)
Adjusted rate	84.3%	80.0%	55.8%	55.2%
Terminal rate	27/33 (82%)	25/35 (71%)	19/38 (50%)	23/42 (55%)
First incidence (days)	386	506	501	697
Poly-3 test	P<0.001N	P=0.387N	P=0.002N	P<0.001N

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, and spleen; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

Table D4
Historical Incidence of Alveolar/bronchiolar Neoplasms in Control Female $B6C3F_1$ Mice[a]

Study	Incidence in Controls Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence: Inhalation Studies			
Decalin	1/49	6/49	7/49
Divinylbenzene	4/50	2/50	6/50
Indium phosphide	3/50	1/50	4/50
Methyl isobutyl ketone	4/50	0/50	4/50
Propylene glycol mono-*t*-butyl ether	2/50	1/50	3/50
Stoddard solvent IIC	2/50	0/50	2/50
Vanadium pentoxide	1/50	0/50	1/50
Overall Historical Incidence: Inhalation Studies			
Total (%)	17/349 (4.9%)	10/349 (2.9%)	27/349 (7.7%)
Mean ± standard deviation	4.9% ± 2.5%	2.9% ± 4.4%	7.8% ± 4.3%
Range	2%-8%	0%-12%	2%-14%
Overall Historical Incidence: All Routes			
Total (%)	80/1,552 (5.2%)	40/1,552 (2.6%)	117/1,552 (7.5%)
Mean ± standard deviation	5.1% ± 3.5%	2.5% ± 2.6%	7.4% ± 3.8%
Range	0%-12%	0%-12%	0%-14%

[a] Data as of January 28, 2005

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	10 ppm	30 ppm	100 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death			1	
Moribund	11	12	8	7
Natural deaths	6	3	3	1
Survivors				
Terminal sacrifice	33	35	38	42
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Infiltration cellular, mixed cell				1 (2%)
Gallbladder	(45)	(41)	(36)	(41)
Hemorrhage, chronic	1 (2%)			
Inflammation, acute			1 (3%)	
Inflammation, chronic				1 (2%)
Intestine large, rectum	(46)	(48)	(50)	(50)
Artery, inflammation, chronic active	1 (2%)			
Liver	(49)	(50)	(50)	(50)
Angiectasis	1 (2%)			
Basophilic focus	4 (8%)	2 (4%)		2 (4%)
Clear cell focus	4 (8%)	2 (4%)	3 (6%)	
Eosinophilic focus	12 (24%)	8 (16%)	3 (6%)	4 (8%)
Fatty change	2 (4%)	1 (2%)		
Hematopoietic cell proliferation		1 (2%)	1 (2%)	1 (2%)
Infarct		1 (2%)		
Inflammation, acute			1 (2%)	
Inflammation, chronic				1 (2%)
Inflammation, granulomatous	1 (2%)		1 (2%)	
Mixed cell focus				1 (2%)
Necrosis	1 (2%)		3 (6%)	1 (2%)
Tension lipidosis	1 (2%)	5 (10%)	2 (4%)	4 (8%)
Vacuolization cytoplasmic, focal				1 (2%)
Centrilobular, hypertrophy	1 (2%)			
Mesentery	(17)	(16)	(4)	(5)
Artery, inflammation, chronic active	1 (6%)			
Fat, congestion		1 (6%)		
Fat, hemorrhage			1 (25%)	
Fat, necrosis	17 (100%)	15 (94%)	3 (75%)	5 (100%)
Pancreas	(48)	(50)	(50)	(50)
Atrophy		2 (4%)	1 (2%)	
Basophilic focus			1 (2%)	
Duct, cyst			2 (4%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Hyperplasia, squamous	3 (6%)	5 (10%)		1 (2%)
Inflammation, chronic active	1 (2%)			2 (4%)
Ulcer		1 (2%)	1 (2%)	
Stomach, glandular	(49)	(50)	(49)	(49)
Hemorrhage		1 (2%)		
Necrosis	1 (2%)			
Tooth	(9)	(13)	(8)	(15)
Incisor, dysplasia	9 (100%)	13 (100%)	8 (100%)	15 (100%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Cardiovascular System				
Blood vessel	(1)			
Aorta, mineralization	1 (100%)			
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	3 (6%)	6 (12%)	1 (2%)	1 (2%)
Infiltration cellular, polymorphonuclear			1 (2%)	
Inflammation, suppurative		1 (2%)		
Mineralization	1 (2%)	1 (2%)		1 (2%)
Necrosis			1 (2%)	
Thrombosis		1 (2%)		
Artery, inflammation, chronic active	2 (4%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia	1 (2%)	2 (4%)	5 (10%)	4 (8%)
Hypertrophy		3 (6%)	2 (4%)	8 (16%)
Adrenal medulla	(49)	(50)	(49)	(50)
Hyperplasia	1 (2%)	1 (2%)		2 (4%)
Necrosis	1 (2%)			
Islets, pancreatic	(48)	(49)	(49)	(50)
Hyperplasia			1 (2%)	
Pituitary gland	(47)	(50)	(49)	(45)
Cyst				1 (2%)
Pars distalis, angiectasis	3 (6%)			
Pars distalis, hyperplasia	8 (17%)	16 (32%)	6 (12%)	5 (11%)
Thyroid gland	(49)	(49)	(50)	(48)
C-cell, hyperplasia		1 (2%)		
Follicular cell, hyperplasia	1 (2%)	2 (4%)		1 (2%)
General Body System				
None				
Genital System				
Ovary	(48)	(50)	(49)	(49)
Angiectasis	2 (4%)	3 (6%)		
Cyst	9 (19%)	14 (28%)	10 (20%)	9 (18%)
Inflammation, acute			1 (2%)	
Mineralization	1 (2%)			
Necrosis			1 (2%)	
Thrombosis				1 (2%)
Uterus	(49)	(50)	(50)	(49)
Angiectasis		1 (2%)	2 (4%)	1 (2%)
Endometrium, hyperplasia, cystic	2 (4%)	8 (16%)	5 (10%)	8 (16%)

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Hematopoietic System				
Lymph node	(9)	(3)	(5)	(2)
Ectasia	1 (11%)			
Deep cervical, hyperplasia, lymphoid	1 (11%)			
Deep cervical, infiltration cellular, plasma cell				1 (50%)
Iliac, angiectasis				1 (50%)
Iliac, ectasia	1 (11%)			
Lumbar, angiectasis			1 (20%)	
Renal, angiectasis			1 (20%)	
Lymph node, mesenteric	(49)	(50)	(49)	(49)
Angiectasis	1 (2%)			
Ectasia			1 (2%)	
Inflammation, granulomatous		1 (2%)		
Spleen	(49)	(50)	(49)	(49)
Hematopoietic cell proliferation	3 (6%)	3 (6%)	3 (6%)	1 (2%)
Inflammation, acute			1 (2%)	
Necrosis			1 (2%)	
Sinusoid, dilatation				1 (2%)
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Inflammation, chronic active	3 (6%)	2 (4%)		1 (2%)
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Degeneration, focal				1 (2%)
Hemorrhage		1 (2%)		
Meninges, infiltration cellular, mononuclear cell	1 (2%)	1 (2%)		

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Divinylbenzene-HP

	Chamber Control	10 ppm	30 ppm	100 ppm
Respiratory System				
Larynx	(48)	(50)	(50)	(49)
Hyperplasia, squamous				1 (2%)
Inflammation, suppurative		1 (2%)		1 (2%)
Lung	(50)	(50)	(50)	(49)
Hemorrhage	1 (2%)			
Infiltration cellular, polymorphonuclear			1 (2%)	
Inflammation, acute			1 (2%)	
Thrombosis			1 (2%)	
Alveolar epithelium, hyperplasia	4 (8%)	3 (6%)	4 (8%)	8 (16%)
Alveolus, granuloma			1 (2%)	
Alveolus, infiltration cellular, histiocyte	3 (6%)	6 (12%)	9 (18%)	17 (35%)
Bronchiole, hyperplasia				1 (2%)
Bronchiole, hyperplasia, atypical		39 (78%)	45 (90%)	48 (98%)
Nose	(50)	(50)	(50)	(49)
Inflammation, suppurative	1 (2%)	50 (100%)	49 (98%)	49 (100%)
Glands, respiratory epithelium, metaplasia	3 (6%)	50 (100%)	50 (100%)	49 (100%)
Olfactory epithelium, atrophy	8 (16%)			
Olfactory epithelium, degeneration, hyaline	2 (4%)	50 (100%)	40 (80%)	8 (16%)
Olfactory epithelium, respiratory epithelium, metaplasia		50 (100%)	50 (100%)	49 (100%)
Trachea	(49)	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)		
Special Senses System				
Eye	(50)	(50)	(50)	(49)
Cataract	1 (2%)	2 (4%)		1 (2%)
Inflammation				1 (2%)
Phthisis bulbi	1 (2%)	1 (2%)		
Cornea, hyperplasia, squamous			1 (2%)	
Cornea, inflammation, chronic active	1 (2%)	3 (6%)		3 (6%)
Cornea, inflammation, suppurative				1 (2%)
Cornea, mineralization				6 (12%)
Harderian gland	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	4 (8%)	2 (4%)	3 (6%)
Inflammation, chronic active	1 (2%)			
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Amyloid deposition		1 (2%)		
Infarct			1 (2%)	
Inflammation, suppurative		2 (4%)	2 (4%)	
Metaplasia, osseous	2 (4%)	3 (6%)	3 (6%)	1 (2%)
Mineralization	1 (2%)			
Nephropathy	25 (51%)	31 (62%)	22 (44%)	17 (34%)
Artery, inflammation, chronic active				1 (2%)
Urinary bladder	(49)	(50)	(50)	(49)
Inflammation, suppurative			1 (2%)	
Artery, inflammation, chronic active	1 (2%)			

APPENDIX E
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

Salmonella typhimurium Mutagenicity Test Protocol

Three independent mutagenicity assays were conducted with divinylbenzene. Testing was performed for the first two assays with divinylbenzene of unknown purity as reported by Zeiger *et al.* (1987). The third assay, conducted with the same lot of divinylbenzene (80%) tested in the 2-year study, used a slightly modified protocol (activation only with rat liver S9) and also employed *Escherichia coli* strain WP2 uvrA pKM101 as a bacterial tester strain in addition to *Salmonella typhimurium* strains. Divinylbenzene was sent to the laboratories as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, TA1535, and TA1537 and with the *E. coli* tester strain either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of divinylbenzene. The high dose was limited by toxicity. All trials were repeated at the same or a higher S9 fraction.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose-related, is not reproducible, or is not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

Mouse Peripheral Blood Micronucleus Test Protocol

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). At the end of the 3-month toxicity study, peripheral blood samples were obtained from male and female mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with acridine orange and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 normochromatic erythrocytes (NCEs) in each of 10 animals per exposure group. In addition, the percentage of polychromatic erythrocytes (PCEs) in a population of 1,000 erythrocytes was determined as a measure of bone marrow toxicity.

The results were tabulated as the mean of the pooled results from all animals within an exposure group plus or minus the standard error of the mean. The frequency of micronucleated cells among NCEs was analyzed by a statistical software package that tested for increasing trend over exposure groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each exposure group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single exposed group is less than or equal to 0.025 divided by the number of exposed groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Results of the 3-month study were accepted without repeat tests, because additional test data could not be obtained. Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

Evaluation Protocol

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and different results were obtained among aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the *in vitro* assays have another variable that must be considered in arriving at an overall test result. *In vitro* assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgement of the overall evidence for activity of the chemical in an assay.

Results

Divinylbenzene was not mutagenic in *S. typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537 or the *E. coli* tester strain WP2 uvrA when tested with and without induced hamster or rat liver S9 in any of three independently conducted assays (Tables E1 and E2; Zeiger *et al.*, 1987). The highest concentration tested at one laboratory was 100 µg/plate; the other two laboratories tested higher concentrations, up to 1,000 µg/plate. It should be considered that inadequate exposure of the tester strains may have occurred, as incubation with this volatile compound was not carried out within the closed environment of a desiccator. No increases in the frequencies of micronucleated NCEs or alterations in the percentages of PCEs were seen in peripheral blood of male or female $B6C3F_1$ mice exposed to divinylbenzene by inhalation for 3 months (Table E2).

Table E1
Mutagenicity of Divinylbenzene in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/Plate[b] −S9 Trial 1	−S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
Study performed at BioReliance Corporation							
TA100	0	123 ± 3.7	129 ± 3.8	118 ± 6.2	122 ± 4.0	134 ± 6.6	115 ± 5.5
	0.3	120 ± 10.4	117 ± 4.0				
	1	137 ± 3.8	112 ± 5.7	103 ± 10.0	104 ± 8.3	119 ± 5.8	116 ± 7.5
	3.3	135 ± 6.7	124 ± 6.3	132 ± 1.9	102 ± 8.4	128 ± 4.3	102 ± 9.8
	10	127 ± 3.3	108 ± 6.8	112 ± 10.0	105 ± 7.6	147 ± 9.3	112 ± 5.5
	33	125 ± 4.7[c]	114 ± 11.8[c]	112 ± 10.5	119 ± 9.3	126 ± 3.5	120 ± 3.0
	100			112 ± 10.2[c]	100 ± 10.2	126 ± 3.3[c]	105 ± 5.0
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		1,293 ± 27.1	1,434 ± 27.9	1,022 ± 8.5	1,017 ± 49.6	969 ± 21.7	702 ± 5.8
TA1535	0	35 ± 2.4	36 ± 0.9	10 ± 0.9	14 ± 0.6	16 ± 1.2	15 ± 2.2
	0.3	28 ± 3.4	33 ± 5.5				
	1	30 ± 3.4	33 ± 1.2	12 ± 4.0	12 ± 2.5	16 ± 2.6	20 ± 2.2
	3.3	34 ± 3.0	40 ± 2.3	9 ± 0.7	21 ± 1.7	15 ± 1.3	19 ± 1.5
	10	30 ± 3.8	30 ± 0.7	14 ± 0.9	18 ± 2.6	15 ± 2.6	16 ± 1.9
	33	29 ± 1.2[c]	37 ± 3.3[c]	13 ± 1.2	15 ± 1.9	13 ± 2.6	12 ± 0.6
	100			8 ± 0.0[c]	13 ± 2.6[c]	14 ± 1.5[c]	16 ± 1.8[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		988 ± 3.7	1,053 ± 31.3	110 ± 4.4	247 ± 12.3	136 ± 9.1	167 ± 15.2
TA97	0	105 ± 1.2	117 ± 6.6	131 ± 1.2	185 ± 9.3	145 ± 11.7	211 ± 12.7
	0.3	114 ± 4.8	111 ± 8.2				
	1	92 ± 5.0	95 ± 5.0	120 ± 9.6	200 ± 7.0	170 ± 6.2	225 ± 3.8
	3.3	92 ± 1.2	95 ± 1.5	128 ± 3.9	206 ± 5.2	171 ± 8.9	228 ± 10.1
	10	86 ± 9.3	99 ± 3.8	136 ± 10.1	179 ± 13.1	160 ± 4.3	201 ± 3.5
	33	101 ± 5.8[c]	100 ± 3.2[c]	131 ± 4.7	215 ± 8.4	180 ± 4.2	222 ± 14.5
	100			129 ± 6.1[c]	208 ± 2.3[c]	147 ± 8.2[c]	192 ± 5.8[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		592 ± 26.3	1,198 ± 59.0	664 ± 30.9	789 ± 38.4	644 ± 13.8	499 ± 34.2
TA98	0	18 ± 1.5	18 ± 3.6	32 ± 0.9	31 ± 3.8	34 ± 0.6	33 ± 4.5
	0.3	16 ± 1.8	17 ± 0.9				
	1	14 ± 1.7	16 ± 3.6	28 ± 4.3	30 ± 3.9	30 ± 1.2	32 ± 3.9
	3.3	18 ± 2.6	18 ± 1.5	34 ± 3.5	36 ± 1.0	31 ± 1.2	37 ± 3.7
	10	15 ± 1.7	20 ± 2.5	37 ± 4.4	37 ± 6.1	41 ± 1.9	34 ± 4.5
	33	17 ± 1.2[c]	14 ± 2.0[c]	35 ± 1.2	31 ± 0.3	32 ± 4.1	37 ± 1.8
	100			28 ± 2.8[c]	33 ± 2.6	31 ± 1.2[c]	27 ± 4.1
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,489 ± 20.5	2,068 ± 110.6	1,063 ± 27.6	832 ± 129.8	1,028 ± 42.9	372 ± 25.1

Table E1
Mutagenicity of Divinylbenzene in *Salmonella typhimurium*

Strain	Dose (µg/plate)	Revertants/Plate –S9 Trial 1	–S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
Study performed at SRI International							
TA100	0	118 ± 12.3	78 ± 3.4	111 ± 1.8	95 ± 5.3	105 ± 8.5	99 ± 0.3
	0.3		88 ± 4.2				
	1	111 ± 20.0	84 ± 8.0				
	3	111 ± 5.3	89 ± 11.9				
	10	102 ± 14.1	100 ± 11.0	102 ± 7.0	107 ± 4.2	113 ± 8.5	100 ± 0.9
	33	96 ± 13.6	95 ± 14.9	123 ± 5.0	97 ± 8.1	95 ± 4.1	105 ± 4.5
	100	82 ± 3.6[c]		111 ± 0.3	103 ± 8.3	103 ± 14.0	101 ± 0.7
	333			88 ± 2.3	98 ± 5.0	106 ± 3.2	87 ± 0.3
	666				91 ± 7.0[c]		80 ± 6.9[c]
	1,000			7 ± 7.0[c]		48 ± 24.7[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		383 ± 14.9	208 ± 16.4	1,784 ± 26.1	1,024 ± 61.8	922 ± 112.2	438 ± 5.6
TA1535	0	36 ± 1.9	20 ± 3.2	11 ± 2.1	7 ± 0.6	13 ± 3.5	7 ± 0.7
	0.3		18 ± 4.2				
	1	26 ± 5.5	12 ± 4.4				
	3	25 ± 2.9	16 ± 1.5				
	10	24 ± 6.0	15 ± 2.5	7 ± 0.6	7 ± 3.0	8 ± 0.9	6 ± 0.0
	33	11 ± 4.2	8 ± 3.2	6 ± 0.6	7 ± 1.2	9 ± 2.7	6 ± 0.0
	100	0 ± 0.0[c]		8 ± 2.7	6 ± 3.2	7 ± 1.0	7 ± 0.3
	333			6 ± 1.2	4 ± 0.6	6 ± 1.2	7 ± 0.3
	666				5 ± 1.2[c]		3 ± 0.9[c]
	1,000			0 ± 0.0[c]		0 ± 0.0[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		395 ± 21.7	250 ± 13.5	492 ± 17.2	351 ± 10.4	211 ± 18.1	158 ± 11.5
TA1537	0	4 ± 0.9	5 ± 0.0	9 ± 0.9	5 ± 1.0	7 ± 0.3	4 ± 0.9
	0.3		5 ± 1.2				
	1	6 ± 0.6	4 ± 1.2				
	3	7 ± 0.7	4 ± 1.2				
	10	6 ± 2.0	7 ± 0.3	7 ± 2.1	6 ± 1.0	8 ± 0.9	6 ± 1.5
	33	4 ± 0.7	5 ± 0.3	5 ± 0.7	6 ± 2.0	6 ± 1.5	7 ± 0.6
	100	0 ± 0.0[c]		6 ± 1.2	4 ± 1.2	5 ± 0.7	7 ± 1.8
	333			6 ± 0.3	5 ± 1.2	6 ± 0.3	5 ± 0.0
	666				5 ± 0.9[c]		4 ± 2.1[c]
	1,000			0 ± 0.0[c]		0 ± 0.0[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		186 ± 19.4	157 ± 28.2	408 ± 11.7	354 ± 22.2	132 ± 20.3	114 ± 5.7

Table E1
Mutagenicity of Divinylbenzene in *Salmonella typhimurium*

Strain	Dose (µg/plate)	Revertants/Plate –S9 Trial 1	–S9 Trial 2	+hamster S9 10%	+hamster S9 10%	+rat S9 10%	+rat S9 10%
Study performed at SRI International (continued)							
TA98	0	21 ± 1.5	16 ± 1.2	36 ± 2.5	36 ± 3.1	23 ± 2.3	20 ± 1.3
	0.3		15 ± 0.6				
	1	17 ± 1.5	13 ± 0.9				
	3	14 ± 1.2	14 ± 0.9				
	10	12 ± 2.2	11 ± 2.1	26 ± 2.7	30 ± 4.2	20 ± 1.9	22 ± 3.1
	33	9 ± 2.4	15 ± 1.7	29 ± 1.2	24 ± 2.0	32 ± 3.0	22 ± 1.8
	100	0 ± 0.0[c]		24 ± 2.0	19 ± 3.5	25 ± 3.5	18 ± 2.1
	333			29 ± 2.1	24 ± 7.9	25 ± 2.0	25 ± 3.4
	666				15 ± 1.5[c]		17 ± 1.7[c]
	1,000			0 ± 0.0[c]		0 ± 0.0[c]	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		475 ± 5.4	325 ± 9.7	1,629 ± 25.7	948 ± 61.4	867 ± 11.9	386 ± 14.6

[a] The detailed protocol and these data are presented by Zeiger *et al*. (1987). 0 µg/plate was the solvent control. Purity of divinylbenzene not known.
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97 and TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

Table E2
Mutagenicity of Divinylbenzene-HP (80%) in *Salmonella typhimurium*

Strain	Dose (µg/plate)	Revertants/Plate[b] –S9 Trial 1	–S9 Trial 2	+ 10% rat S9 Trial 1	+ 10% rat S9 Trial 2
TA100	0	42 ± 7.4	50 ± 4.0	45 ± 4.2	43 ± 9.9
	5		46 ± 3.3		
	10	53 ± 6.4	47 ± 5.8		
	25	57 ± 3.0	36 ± 4.3		
	50	43 ± 2.6	33 ± 1.0	38 ± 1.2	37 ± 2.6
	75	42 ± 4.3	45 ± 1.5		
	100	37 ± 1.2		46 ± 5.5	45 ± 6.2
	250			54 ± 2.4	52 ± 3.0
	500			43 ± 3.5	28 ± 4.3
	750			53 ± 8.1	17 ± 0.9
Trial summary		Negative	Negative	Negative	Negative
Positive control[c]		531 ± 12.4	512 ± 32.0	692 ± 11.3	629 ± 11.0
TA98	0	17 ± 0.9	12 ± 0.7	18 ± 1.8	19 ± 1.7
	5	11 ± 2.7	11 ± 0.6		
	10	11 ± 1.5	11 ± 0.9		
	25	14 ± 1.2	10 ± 0.3		
	50	13 ± 2.0	7 ± 1.3	16 ± 2.9	18 ± 2.7
	75	7 ± 2.4	5 ± 1.2		
	100			12 ± 3.9	12 ± 0.9
	250			23 ± 2.0	14 ± 1.5
	500			16 ± 2.8	18 ± 1.2
	750			7 ± 2.9	12 ± 2.3
Trial summary		Negative	Negative	Negative	Negative
Positive control		516 ± 2.8	412 ± 4.4	874 ± 73.0	770 ± 17.7
***Escherichia coli* WPM uvrA pKM101 (Analogous to TA102)**					
	0	109 ± 2.9	129 ± 4.9	164 ± 17.5	140 ± 5.8
	5	140 ± 3.5	117 ± 8.1		
	10	139 ± 7.0	109 ± 4.6		
	25	109 ± 6.4	109 ± 3.8		
	50	125 ± 6.0	107 ± 3.7	195 ± 16.7	127 ± 14.8
	75	107 ± 2.3	99 ± 5.7		
	100			179 ± 1.9	128 ± 13.1
	250			154 ± 3.5	141 ± 6.7
	500			134 ± 3.3	136 ± 8.8
	750			144 ± 17.7	129 ± 7.8
Trial summary		Negative	Negative	Negative	Negative
Positive control		1,343 ± 26.3	949 ± 74.6	850 ± 20.8	1,205 ± 25.7

[a] Study performed at SITEK Research Laboratories. The detailed protocol is presented by Zeiger *et al*. (1987). 0 µg/plate was the solvent control.

[b] Revertants are presented as mean ± standard error from three plates.

[c] The positive controls in the absence of metabolic activation were sodium azide (TA100), 4-nitro-*o*-phenylenediamine (TA98), and methyl methanesulfonate (pKM101). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E3
Frequency of Micronuclei in Normochromatic Erythrocytes and Percent Polychromatic Erythrocytes in Peripheral Blood of Mice Following Exposure to Divinylbenzene-HP by Inhalation for 3 Months[a]

Compound	Exposure Concentration (ppm)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/ 1,000 NCEs[b]	P-Value[c]	PCEs[b] (%)
Male					
Air[d]	0	10	1.60 ± 0.12		1.9 ± 0.1
Divinylbenzene	12.5	10	1.30 ± 0.15	0.7848	1.9 ± 0.1
	25	10	1.40 ± 0.21	0.6973	1.6 ± 0.2
	50	10	1.55 ± 0.26	0.5502	1.6 ± 0.2
	100	10	1.40 ± 0.22	0.6973	1.6 ± 0.1
	200	0[e]			
			P=0.558[f]		
Female					
Air	0	10	1.40 ± 0.2		1.6 ± 0.13
Divinylbenzene	12.5	10	1.05 ± 0.16	0.8415	1.7 ± 0.1
	25	10	1.05 ± 0.16	0.8415	1.6 ± 0.1
	50	10	1.25 ± 0.17	0.6600	1.8 ± 0.1
	100	10	1.15 ± 0.22	0.7582	1.9 ± 0.1
	200	1[e]	1.50		2.1
			P=0.590		

[a] Study was performed at SITEK Research Laboratories. The detailed protocol is presented by MacGregor *et al.* (1990). PCE=polychromatic erythrocyte; NCE=normochromatic erythrocyte.
[b] Mean ± standard error
[c] Pairwise comparison with the untreated control group; significant at P≤0.006 (ILS, 1990)
[d] Untreated control
[e] Excluded from statistical analyses due to high mortality
[f] Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed trend test, significant at P≤0.025 (ILS, 1990)

APPENDIX F
CLINICAL PATHOLOGY RESULTS

TABLE F1 Hematology and Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of Divinylbenzene-HP F-2
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Table F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Male						
Hematology						
Automated hematocrit (%)						
Day 3	40.3 ± 0.6	40.8 ± 0.8	42.0 ± 0.8	41.2 ± 0.5	42.0 ± 0.7	43.2 ± 0.7**
Day 23	46.2 ± 0.6	45.2 ± 0.4	45.1 ± 0.7	45.3 ± 0.7	43.9 ± 0.6	48.5 ± 0.5
Week 14	45.1 ± 0.3	44.9 ± 0.5	45.5 ± 0.3	46.1 ± 0.5	45.6 ± 0.4	46.6 ± 0.4*
Manual hematocrit (%)						
Day 3	42.5 ± 0.5	42.3 ± 0.9	43.4 ± 1.0	43.6 ± 0.6	44.0 ± 0.7	44.7 ± 0.5*
Day 23	47.3 ± 0.5	46.5 ± 0.5	47.2 ± 0.5	47.0 ± 0.6	45.7 ± 0.4	48.7 ± 0.3
Week 14	46.5 ± 0.4	45.8 ± 0.4	45.9 ± 0.2	47.1 ± 0.4	46.0 ± 0.4	47.2 ± 0.3
Hemoglobin (g/dL)						
Day 3	12.7 ± 0.2	12.8 ± 0.3	13.1 ± 0.3	12.9 ± 0.2	13.1 ± 0.3	13.4 ± 0.2
Day 23	15.0 ± 0.1	15.0 ± 0.2	15.0 ± 0.2	14.9 ± 0.2	14.5 ± 0.2	15.4 ± 0.2
Week 14	14.9 ± 0.1	14.8 ± 0.1	14.7 ± 0.1	15.1 ± 0.1	14.8 ± 0.1	15.2 ± 0.0
Erythrocytes (10^6/µL)						
Day 3	6.35 ± 0.10	6.49 ± 0.17	6.68 ± 0.11	6.57 ± 0.08	6.73 ± 0.14*	6.96 ± 0.12**
Day 23	7.34 ± 0.10	7.15 ± 0.10	7.16 ± 0.16	7.25 ± 0.14	7.03 ± 0.14	7.65 ± 0.07
Week 14	8.28 ± 0.06	8.27 ± 0.08	8.36 ± 0.03	8.50 ± 0.09	8.43 ± 0.07	8.57 ± 0.06**
Reticulocytes (10^6/µL)						
Day 3	0.42 ± 0.05	0.49 ± 0.06	0.39 ± 0.06	0.42 ± 0.03	0.45 ± 0.03	0.44 ± 0.04
Day 23	0.17 ± 0.02	0.28 ± 0.03**	0.24 ± 0.02*	0.26 ± 0.02*	0.27 ± 0.03**	0.34 ± 0.03**
Week 14	0.19 ± 0.02	0.19 ± 0.01	0.19 ± 0.02	0.21 ± 0.02	0.19 ± 0.02	0.18 ± 0.03
Nucleated erythrocytes/100 leukocytes						
Day 3	1.00 ± 0.37	1.00 ± 0.37	0.90 ± 0.50	0.90 ± 0.28	1.10 ± 0.53	2.40 ± 0.58
Day 23	0.50 ± 0.31	0.30 ± 0.21	0.40 ± 0.22	0.30 ± 0.21	0.80 ± 0.29	0.40 ± 0.16
Week 14	0.10 ± 0.10	0.20 ± 0.13	0.10 ± 0.10	0.00 ± 0.00	0.10 ± 0.10	0.00 ± 0.00
Mean cell volume (fL)						
Day 3	63.4 ± 0.5	62.8 ± 0.4	62.8 ± 0.3	62.6 ± 0.3	62.6 ± 0.7	62.1 ± 0.3
Day 23	62.9 ± 0.5	63.2 ± 0.5	62.9 ± 0.6	62.6 ± 0.5	62.5 ± 0.7	63.2 ± 0.3
Week 14	54.6 ± 0.2	54.2 ± 0.2	54.4 ± 0.2	54.2 ± 0.1	54.1 ± 0.2	54.4 ± 0.2
Mean cell hemoglobin (pg)						
Day 3	20.0 ± 0.2	19.7 ± 0.2	19.7 ± 0.2	19.7 ± 0.2	19.5 ± 0.3	19.3 ± 0.2
Day 23	20.5 ± 0.3	21.0 ± 0.2	21.0 ± 0.3	20.5 ± 0.3	20.6 ± 0.3	20.1 ± 0.2
Week 14	18.1 ± 0.1	17.9 ± 0.1	17.6 ± 0.1	17.8 ± 0.1	17.5 ± 0.1*	17.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 3	31.6 ± 0.2	31.4 ± 0.3	31.3 ± 0.2	31.3 ± 0.3	31.3 ± 0.3	31.1 ± 0.2
Day 23	32.6 ± 0.4	33.2 ± 0.3	33.3 ± 0.3	32.8 ± 0.3	33.0 ± 0.3	31.7 ± 0.4
Week 14	33.1 ± 0.2	33.0 ± 0.2	32.4 ± 0.2	32.8 ± 0.2	32.4 ± 0.2	32.6 ± 0.3
Platelets (10^3/µL)						
Day 3	890.1 ± 16.9	908.9 ± 18.2	923.5 ± 24.7	936.4 ± 13.7	910.9 ± 31.5	988.1 ± 17.8**
Day 23	852.6 ± 26.1	867.4 ± 47.5	926.1 ± 42.3	940.6 ± 49.0	914.4 ± 35.2	963.7 ± 32.8
Week 14	589.2 ± 7.7	557.7 ± 8.5	557.8 ± 12.9	552.4 ± 12.0	580.8 ± 8.2	602.3 ± 13.5
Leukocytes (10^3/µL)						
Day 3	8.43 ± 0.65	9.29 ± 0.79	9.01 ± 0.47	10.36 ± 0.54	7.26 ± 0.40	5.93 ± 0.49*
Day 23	12.45 ± 0.37	13.23 ± 0.54	12.91 ± 0.48	12.43 ± 0.57	11.19 ± 0.49	7.49 ± 0.61**
Week 14	7.19 ± 0.31	7.35 ± 0.41	6.91 ± 0.31	7.09 ± 0.31	6.78 ± 0.27	7.07 ± 0.40
Segmented neutrophils (10^3/µL)						
Day 3	0.77 ± 0.09	0.99 ± 0.10	1.13 ± 0.10	1.28 ± 0.14*	1.00 ± 0.11	1.25 ± 0.15
Day 23	0.98 ± 0.16	1.13 ± 0.14	1.31 ± 0.12	1.15 ± 0.13	0.94 ± 0.12	0.96 ± 0.08
Week 14	1.12 ± 0.09	1.20 ± 0.08	1.11 ± 0.11	0.99 ± 0.05	0.96 ± 0.06	1.02 ± 0.10

Table F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of Divinylbenzene-HP

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Male (continued)						
Hematology (continued)						
Bands ($10^3/\mu L$)						
Day 3	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Day 23	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes ($10^3/\mu L$)						
Day 3	7.42 ± 0.54	7.94 ± 0.65	7.47 ± 0.51	8.65 ± 0.46	6.04 ± 0.45	4.63 ± 0.48**
Day 23	11.28 ± 0.40	11.98 ± 0.59	11.39 ± 0.37	11.16 ± 0.54	9.72 ± 0.46	6.47 ± 0.57**
Week 14	6.01 ± 0.29	6.09 ± 0.40	5.71 ± 0.29	5.93 ± 0.33	5.67 ± 0.25	5.91 ± 0.40
Monocytes ($10^3/\mu L$)						
Day 3	0.17 ± 0.06	0.36 ± 0.09	0.39 ± 0.09	0.39 ± 0.08	0.21 ± 0.04	0.06 ± 0.02
Day 23	0.11 ± 0.04	0.05 ± 0.03	0.14 ± 0.06	0.08 ± 0.04	0.45 ± 0.10	0.05 ± 0.02
Week14	0.04 ± 0.02	0.04 ± 0.02	0.06 ± 0.02	0.09 ± 0.02	0.08 ± 0.03	0.09 ± 0.03
Basophils ($10^3/\mu L$)						
Day 3	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 23	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.006 ± 0.006	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils ($10^3/\mu L$)						
Day 3	0.08 ± 0.05	0.01 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Day 23	0.08 ± 0.04	0.08 ± 0.03	0.05 ± 0.02	0.05 ± 0.02	0.09 ± 0.04	0.01 ± 0.01
Week 14	0.02 ± 0.02	0.02 ± 0.01	0.03 ± 0.01	0.08 ± 0.02	0.09 ± 0.04	0.04 ± 0.02
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 3	6.3 ± 0.5	5.7 ± 0.3	7.2 ± 0.5	12.0 ± 0.5**	17.8 ± 0.9**	21.9 ± 0.2**
Day 23	9.1 ± 0.3	7.8 ± 0.3	8.3 ± 0.4	10.0 ± 0.6	13.5 ± 0.5**	21.1 ± 0.4**
Week 14	12.6 ± 0.6	11.9 ± 0.5	12.9 ± 0.6	12.9 ± 0.3	11.1 ± 0.6	10.2 ± 0.4**
Creatinine (mg/dL)						
Day 3	0.55 ± 0.02	0.56 ± 0.02[b]	0.59 ± 0.02	0.61 ± 0.01*	0.62 ± 0.02**	0.60 ± 0.02*
Day 23	0.77 ± 0.02	0.72 ± 0.01	0.74 ± 0.02	0.74 ± 0.02	0.72 ± 0.02	0.79 ± 0.01
Week 14	0.71 ± 0.03	0.69 ± 0.02	0.78 ± 0.03	0.79 ± 0.03	0.74 ± 0.02	0.75 ± 0.02
Total protein (g/dL)						
Day 3	5.5 ± 0.1	5.5 ± 0.1	5.5 ± 0.1	5.5 ± 0.1	5.5 ± 0.1	5.7 ± 0.1
Day 23	6.1 ± 0.1	5.9 ± 0.0**	5.9 ± 0.1*	5.8 ± 0.0**	5.7 ± 0.1**	5.7 ± 0.0**
Week 14	6.7 ± 0.1	6.6 ± 0.1	6.7 ± 0.0	6.6 ± 0.1	6.5 ± 0.1	6.5 ± 0.1
Albumin (g/dL)						
Day 3	3.5 ± 0.1	3.4 ± 0.1	3.5 ± 0.1	3.4 ± 0.0	3.4 ± 0.1	3.6 ± 0.0
Day 23	3.9 ± 0.1	3.7 ± 0.1	3.8 ± 0.0	3.8 ± 0.1	3.7 ± 0.1	3.7 ± 0.1
Week 14	4.0 ± 0.0	3.9 ± 0.0	3.9 ± 0.0	3.9 ± 0.0	3.9 ± 0.1	3.9 ± 0.0
Globulin (g/dL)						
Day 3	2.1 ± 0.1	2.1 ± 0.1	2.1 ± 0.0	2.1 ± 0.1	2.1 ± 0.1	2.1 ± 0.0
Day 23	2.3 ± 0.1	2.2 ± 0.1	2.1 ± 0.1	2.0 ± 0.1*	2.0 ± 0.1*	2.0 ± 0.1*
Week 14	2.7 ± 0.1	2.7 ± 0.1	2.8 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.6 ± 0.1
Albumin/globulin ratio						
Day 3	1.7 ± 0.1	1.6 ± 0.1	1.6 ± 0.0	1.6 ± 0.1	1.7 ± 0.1	1.7 ± 0.0
Day 23	1.7 ± 0.1	1.8 ± 0.1	1.8 ± 0.1	2.0 ± 0.1	1.9 ± 0.1	2.0 ± 0.1
Week 14	1.4 ± 0.0	1.5 ± 0.0	1.4 ± 0.1	1.4 ± 0.1	1.5 ± 0.1	1.5 ± 0.1

Table F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of Divinylbenzene-HP

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Male (continued)						
Clinical Chemistry (continued)						
Alanine aminotransferase (IU/L)						
Day 3	52 ± 1	51 ± 3	52 ± 2	51 ± 1	50 ± 1	51 ± 1
Day 23	40 ± 1	35 ± 1**	36 ± 1**	35 ± 1**	34 ± 1**	34 ± 1**
Week 14	93 ± 11	93 ± 8	70 ± 3	86 ± 8	59 ± 5**	44 ± 1**
Alkaline phosphatase (IU/L)						
Day 3	890 ± 20	854 ± 31	867 ± 36	749 ± 32**	767 ± 22**	721 ± 24**
Day 23	570 ± 11	567 ± 17	594 ± 15	587 ± 22	597 ± 21	599 ± 20
Week 14	350 ± 5	322 ± 4*	320 ± 10*	336 ± 7	326 ± 4	314 ± 11*
Creatine kinase (IU/L)						
Day 3	320 ± 32[b]	491 ± 89	394 ± 59	422 ± 69	533 ± 91	405 ± 48
Day 23	346 ± 38	493 ± 100	579 ± 163	405 ± 83	390 ± 38	484 ± 115
Week 14	130 ± 20	154 ± 27	209 ± 33	210 ± 32	192 ± 18	191 ± 29
Sorbitol dehydrogenase (IU/L)						
Day 3	14 ± 1	14 ± 1	14 ± 1	14 ± 1	14 ± 1	13 ± 0
Day 23	13 ± 1	11 ± 1	14 ± 1	12 ± 1	12 ± 1	12 ± 0
Week 14	26 ± 2	27 ± 2	23 ± 1	26 ± 3	19 ± 1*	17 ± 1**
Bile acids (µmol/L)						
Day 3	30.2 ± 2.0	29.3 ± 3.0[c]	25.3 ± 1.3	20.9 ± 1.9*	28.8 ± 5.5[b]	32.4 ± 2.4
Day 23	19.7 ± 0.6	20.3 ± 1.8	21.6 ± 2.1	22.0 ± 1.7	19.0 ± 1.4	22.3 ± 1.4
Week 14	21.5 ± 1.3	20.1 ± 0.9	21.5 ± 2.6	24.5 ± 3.8	20.2 ± 0.9	23.4 ± 2.9
Female						
Hematology						
Automated hematocrit (%)						
Day 3	41.5 ± 0.9	43.1 ± 0.9	42.3 ± 1.0	44.7 ± 0.9	44.0 ± 0.8	44.6 ± 0.8
Day 23	47.7 ± 0.5	47.3 ± 0.5	47.5 ± 0.7	46.4 ± 0.6	47.6 ± 0.5	49.3 ± 0.4
Week 14	44.0 ± 0.2	44.2 ± 0.2	43.7 ± 0.3	44.8 ± 0.3	44.0 ± 0.3	44.8 ± 0.4
Manual hematocrit (%)						
Day 3	43.8 ± 0.8	44.5 ± 0.8	44.7 ± 1.0	46.4 ± 0.9	45.2 ± 0.7	45.4 ± 0.7
Day 23	50.2 ± 0.5	49.6 ± 0.3	49.4 ± 0.6	49.3 ± 0.6	49.5 ± 0.3	50.9 ± 0.6
Week 14	44.3 ± 0.3	44.5 ± 0.3	43.9 ± 0.3	45.2 ± 0.3	44.6 ± 0.3	45.5 ± 0.4
Hemoglobin (g/dL)						
Day 3	13.2 ± 0.3	13.6 ± 0.3	13.4 ± 0.4	13.9 ± 0.4	13.7 ± 0.3	13.8 ± 0.2
Day 23	16.0 ± 0.2	16.1 ± 0.2	15.9 ± 0.2	15.7 ± 0.3	15.7 ± 0.1	16.3 ± 0.1
Week 14	14.7 ± 0.1	14.6 ± 0.1	14.5 ± 0.1	14.9 ± 0.1	14.6 ± 0.1	14.9 ± 0.1
Erythrocytes (10^6/µL)						
Day 3	6.65 ± 0.18	6.90 ± 0.16	6.79 ± 0.19	7.18 ± 0.17*	7.08 ± 0.13*	7.21 ± 0.15*
Day 23	7.38 ± 0.14	7.42 ± 0.12	7.36 ± 0.14	7.36 ± 0.09	7.51 ± 0.09	7.84 ± 0.11
Week 14	7.57 ± 0.03	7.59 ± 0.04	7.53 ± 0.04	7.71 ± 0.05	7.60 ± 0.05	7.75 ± 0.07
Reticulocytes (10^6/µL)						
Day 3	0.39 ± 0.03	0.30 ± 0.03	0.49 ± 0.05	0.43 ± 0.03	0.42 ± 0.04	0.50 ± 0.05
Day 23	0.15 ± 0.02	0.16 ± 0.02	0.17 ± 0.02	0.20 ± 0.02	0.16 ± 0.01	0.15 ± 0.02
Week 14	0.15 ± 0.01	0.18 ± 0.01	0.16 ± 0.01	0.13 ± 0.01	0.14 ± 0.02	0.14 ± 0.01

Table F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of Divinylbenzene-HP

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Female (continued)						
Hematology (continued)						
Nucleated erythrocytes/100 leukocytes						
Day 3	1.20 ± 0.29	0.50 ± 0.22	0.10 ± 0.10*	0.20 ± 0.13	0.60 ± 0.34	3.00 ± 0.84
Day 23	0.20 ± 0.13	0.10 ± 0.10	0.00 ± 0.00	0.10 ± 0.10	0.00 ± 0.00	0.20 ± 0.13
Week 14	0.30 ± 0.21	0.20 ± 0.13	0.40 ± 0.31	0.30 ± 0.15	0.20 ± 0.13	0.10 ± 0.10
Mean cell volume (fL)						
Day 3	62.6 ± 0.4	62.3 ± 0.2	62.4 ± 0.5	62.2 ± 0.4	62.1 ± 0.2	61.8 ± 0.3
Day 23	64.7 ± 0.8	63.8 ± 0.7	64.7 ± 0.9	63.2 ± 0.7	63.3 ± 0.8	62.9 ± 1.0
Week 14	58.1 ± 0.1	58.3 ± 0.3	58.1 ± 0.2	58.0 ± 0.0	57.8 ± 0.3	57.8 ± 0.1
Mean cell hemoglobin (pg)						
Day 3	19.8 ± 0.2	19.8 ± 0.2	19.8 ± 0.2	19.4 ± 0.2	19.4 ± 0.2	19.1 ± 0.2*
Day 23	21.7 ± 0.2	21.7 ± 0.3	21.6 ± 0.3	21.3 ± 0.3	20.9 ± 0.3	20.8 ± 0.3
Week 14	19.4 ± 0.1	19.2 ± 0.1	19.2 ± 0.1	19.3 ± 0.1	19.2 ± 0.1	19.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 3	31.7 ± 0.3	31.7 ± 0.4	31.7 ± 0.3	31.2 ± 0.4	31.1 ± 0.3	30.9 ± 0.3
Day 23	33.5 ± 0.3	34.0 ± 0.3	33.4 ± 0.3	33.8 ± 0.3	33.0 ± 0.3	33.1 ± 0.2
Week 14	33.3 ± 0.1	32.9 ± 0.2	33.2 ± 0.1	33.2 ± 0.2	33.2 ± 0.1	33.1 ± 0.2
Platelets (10^3/µL)						
Day 3	790.5 ± 29.7	834.6 ± 30.6	844.4 ± 13.9	880.6 ± 35.9*	916.5 ± 19.1**	886.4 ± 8.3**
Day 23	845.2 ± 38.3	859.6 ± 26.1	881.2 ± 32.2	834.8 ± 36.6	903.3 ± 36.8	952.5 ± 36.4
Week 14	575.4 ± 7.1	561.1 ± 15.4	579.6 ± 6.8	593.3 ± 21.3	591.2 ± 15.2	598.7 ± 7.4
Leukocytes (10^3/µL)						
Day 3	8.38 ± 0.79	10.11 ± 0.67	9.02 ± 0.70	10.00 ± 0.77	6.89 ± 0.66	5.41 ± 0.58*
Day 23	13.86 ± 0.52	14.06 ± 0.42	12.76 ± 0.35	12.08 ± 0.46*	11.63 ± 0.40**	8.76 ± 0.54**
Week 14	6.54 ± 0.27	6.69 ± 0.36	6.73 ± 0.27	7.74 ± 0.44	6.69 ± 0.31	7.09 ± 0.34
Segmented neutrophils (10^3/µL)						
Day 3	0.73 ± 0.07	0.90 ± 0.15	0.88 ± 0.07	0.97 ± 0.15	0.70 ± 0.08	0.76 ± 0.07
Day 23	0.92 ± 0.09	0.96 ± 0.18	1.29 ± 0.15	0.78 ± 0.14	0.96 ± 0.06	0.96 ± 0.13
Week 14	1.11 ± 0.11	0.97 ± 0.08	1.15 ± 0.13	1.17 ± 0.11	0.98 ± 0.07	0.96 ± 0.10
Bands (10^3/µL)						
Day 3	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Day 23	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/µL)						
Day 3	7.41 ± 0.77	8.94 ± 0.62	7.96 ± 0.68	8.63 ± 0.66	6.08 ± 0.59	4.58 ± 0.57*
Day 23	12.64 ± 0.53	12.95 ± 0.36	11.23 ± 0.28*	11.18 ± 0.42*	10.48 ± 0.43**	7.69 ± 0.54**
Week 14	5.38 ± 0.19	5.64 ± 0.33	5.49 ± 0.28	6.47 ± 0.40	5.59 ± 0.31	6.00 ± 0.31
Monocytes (10^3/µL)						
Day 3	0.21 ± 0.03	0.23 ± 0.07	0.17 ± 0.04	0.35 ± 0.10	0.08 ± 0.03*	0.06 ± 0.02**
Day 23	0.27 ± 0.09	0.13 ± 0.03	0.17 ± 0.04	0.06 ± 0.03	0.11 ± 0.04	0.03 ± 0.02**
Week 14	0.04 ± 0.02	0.06 ± 0.04	0.06 ± 0.02	0.04 ± 0.01	0.07 ± 0.03	0.06 ± 0.03
Basophils (10^3/µL)						
Day 3	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 23	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.008 ± 0.008	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/µL)						
Day 3	0.03 ± 0.02	0.04 ± 0.02	0.02 ± 0.01	0.05 ± 0.02	0.02 ± 0.01	0.01 ± 0.01
Day 23	0.03 ± 0.02	0.03 ± 0.02	0.08 ± 0.04	0.06 ± 0.02	0.08 ± 0.03	0.08 ± 0.03
Week 14	0.01 ± 0.01	0.01 ± 0.01	0.03 ± 0.01	0.06 ± 0.02	0.05 ± 0.02	0.07 ± 0.03

Table F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of Divinylbenzene-HP

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Female (continued)						
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 3	6.8 ± 0.4	7.9 ± 0.3	8.1 ± 0.6	10.9 ± 0.4**	15.4 ± 0.6**	20.7 ± 1.2**
Day 23	9.7 ± 0.4	9.9 ± 0.3	10.0 ± 0.3	10.4 ± 0.3	14.2 ± 0.4**	17.0 ± 0.4**
Week 14	13.7 ± 0.5	13.0 ± 0.9	13.5 ± 0.5	14.2 ± 0.5	12.4 ± 0.5	11.4 ± 0.5*
Creatinine (mg/dL)						
Day 3	0.60 ± 0.02	0.59 ± 0.01	0.66 ± 0.02	0.61 ± 0.01	0.67 ± 0.02	0.62 ± 0.02
Day 23	0.68 ± 0.02	0.65 ± 0.02	0.69 ± 0.01	0.69 ± 0.01	0.68 ± 0.01	0.72 ± 0.01
Week 14	0.75 ± 0.02	0.73 ± 0.02	0.76 ± 0.02	0.78 ± 0.03	0.75 ± 0.02	0.74 ± 0.02
Total protein (g/dL)						
Day 3	5.8 ± 0.1	5.9 ± 0.1	5.7 ± 0.1	5.7 ± 0.1	5.8 ± 0.1	5.8 ± 0.1
Day 23	5.9 ± 0.1	5.9 ± 0.1	6.0 ± 0.0	5.9 ± 0.0	5.8 ± 0.1	6.0 ± 0.1
Week 14	7.0 ± 0.1	6.8 ± 0.1	6.9 ± 0.1	6.8 ± 0.1	6.6 ± 0.1*	6.5 ± 0.1**
Albumin (g/dL)						
Day 3	3.8 ± 0.1	3.7 ± 0.1	3.7 ± 0.1	3.8 ± 0.1	4.0 ± 0.1	3.8 ± 0.1
Day 23	3.9 ± 0.1	3.8 ± 0.1	3.8 ± 0.1	3.7 ± 0.1	3.8 ± 0.1	3.9 ± 0.1
Week 14	4.5 ± 0.0	4.3 ± 0.1	4.5 ± 0.0	4.4 ± 0.1	4.2 ± 0.1**	4.1 ± 0.1**
Globulin (g/dL)						
Day 3	2.0 ± 0.1	2.2 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	1.8 ± 0.1	2.0 ± 0.1
Day 23	2.0 ± 0.1	2.1 ± 0.1	2.2 ± 0.1	2.2 ± 0.1	2.0 ± 0.1	2.1 ± 0.1
Week 14	2.5 ± 0.1	2.5 ± 0.1	2.5 ± 0.1	2.4 ± 0.0	2.5 ± 0.1	2.3 ± 0.1
Albumin/globulin ratio						
Day 3	2.0 ± 0.1	1.7 ± 0.1	2.0 ± 0.1	2.0 ± 0.1	2.3 ± 0.2	2.0 ± 0.2
Day 23	1.9 ± 0.1	1.9 ± 0.1	1.8 ± 0.1	1.7 ± 0.1	1.9 ± 0.1	1.9 ± 0.1
Week 14	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.0	1.7 ± 0.0	1.8 ± 0.1
Alanine aminotransferase (IU/L)						
Day 3	48 ± 2	45 ± 1	47 ± 2	49 ± 1	46 ± 2	45 ± 2
Day 23	34 ± 1	34 ± 1	33 ± 1	32 ± 1	31 ± 1	31 ± 1
Week 14	54 ± 5	53 ± 3	59 ± 7	47 ± 3	49 ± 4	39 ± 1**
Alkaline phosphatase (IU/L)						
Day 3	733 ± 27	717 ± 22	728 ± 25	672 ± 21	683 ± 21	609 ± 16**
Day 23	429 ± 11	431 ± 12	427 ± 16	433 ± 8	437 ± 13	429 ± 13
Week 14	314 ± 7	288 ± 12	291 ± 8	307 ± 9	287 ± 10	280 ± 7*
Creatine kinase (IU/L)						
Day 3	299 ± 20	230 ± 28	391 ± 55	413 ± 71	343 ± 32	357 ± 83
Day 23	292 ± 35[b]	284 ± 46	294 ± 29	253 ± 21	309 ± 72	323 ± 79
Week 14	229 ± 26	247 ± 29	208 ± 17	202 ± 26	228 ± 20	264 ± 29
Sorbitol dehydrogenase (IU/L)						
Day 3	14 ± 1	14 ± 0	15 ± 1	14 ± 1	14 ± 1	14 ± 1
Day 23	14 ± 1	14 ± 0	14 ± 1	15 ± 1	15 ± 1	16 ± 1
Week 14	16 ± 1	16 ± 1	18 ± 2	16 ± 1	15 ± 1	13 ± 0*
Bile acids (µmol/L)						
Day 3	20.1 ± 1.5	16.5 ± 0.9	21.2 ± 1.3	19.8 ± 2.9	22.3 ± 2.1	22.0 ± 2.1
Day 23	16.4 ± 1.8	18.0 ± 2.1	20.0 ± 2.0	16.8 ± 1.1	15.8 ± 1.0	21.1 ± 1.0*
Week 14	18.1 ± 1.6	21.2 ± 3.2	19.4 ± 2.1	16.7 ± 3.4	15.8 ± 1.5	19.0 ± 1.8

* Significantly different (P≤0.05) from the chamber control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9
[c] n=8

Table F2
Hematology Data for Mice in the 3-Month Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	12.5 ppm	25 ppm	50 ppm	100 ppm	200 ppm
Male						
n	10	10	10	10	10	0
Automated hematocrit (%)	49.3 ± 0.4	50.0 ± 0.3	50.0 ± 0.3	49.6 ± 0.4	48.9 ± 0.3	
Manual hematocrit (%)	49.1 ± 0.4	50.0 ± 0.3	49.9 ± 0.3	49.6 ± 0.4	48.7 ± 0.3	
Hemoglobin (g/dL)	15.8 ± 0.1	16.1 ± 0.1	16.2 ± 0.1	16.1 ± 0.1	15.6 ± 0.1	
Erythrocytes (10^6/µL)	10.23 ± 0.07	10.33 ± 0.07	10.38 ± 0.04	10.24 ± 0.09	10.09 ± 0.04	
Reticulocytes (10^6/µL)	0.22 ± 0.01	0.20 ± 0.01	0.21 ± 0.01	0.21 ± 0.01	0.20 ± 0.01	
Nucleated erythrocytes /100 leukocytes	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	
Howell-Jolly bodies (% erythrocytes)	0.0 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	
Mean cell volume (fL)	48.3 ± 0.2	48.3 ± 0.2	48.1 ± 0.2	48.4 ± 0.2	48.6 ± 0.2	
Mean cell hemoglobin (pg)	15.5 ± 0.1	15.6 ± 0.1	15.6 ± 0.1	15.7 ± 0.1	15.4 ± 0.1	
Mean cell hemoglobin concentration (g/dL)	32.1 ± 0.2	32.2 ± 0.1	32.4 ± 0.2	32.4 ± 0.1	31.8 ± 0.2	
Platelets (10^3/µL)	954.2 ± 30.6	895.3 ± 17.3	871.1 ± 16.9	904.5 ± 40.1	912.3 ± 11.1	
Leukocytes (10^3/µL)	2.69 ± 0.27	2.13 ± 0.16	2.53 ± 0.28	2.71 ± 0.19	2.16 ± 0.15	
Segmented neutrophils (10^3/µL)	0.34 ± 0.07	0.23 ± 0.04	0.35 ± 0.05	0.31 ± 0.03	0.30 ± 0.04	
Bands (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	
Lymphocytes (10^3/µL)	2.32 ± 0.23	1.87 ± 0.14	2.14 ± 0.23	2.36 ± 0.18	1.83 ± 0.13	
Monocytes (10^3/µL)	0.00 ± 0.00	0.01 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	
Basophils (10^3/µL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	
Eosinophils (10^3/µL)	0.03 ± 0.01	0.02 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	
Female						
n	10	10	10	10	10	1[b]
Automated hematocrit (%)	51.0 ± 0.4	50.3 ± 0.4	50.0 ± 0.2	49.5 ± 0.4*	49.3 ± 0.3**	44.6
Manual hematocrit (%)	51.0 ± 0.3	50.8 ± 0.3	50.0 ± 0.2*	49.6 ± 0.5*	49.3 ± 0.3**	44.5
Hemoglobin (g/dL)	16.5 ± 0.1	16.4 ± 0.1	16.2 ± 0.1**	16.0 ± 0.1**	16.0 ± 0.1**	14.2
Erythrocytes (10^6/µL)	10.34 ± 0.08	10.05 ± 0.07*	10.10 ± 0.03*	10.06 ± 0.07*	9.91 ± 0.07**	9.01
Reticulocytes (10^6/µL)	0.25 ± 0.02	0.24 ± 0.01	0.21 ± 0.01	0.20 ± 0.01*	0.20 ± 0.01*	0.17
Nucleated erythrocytes /100 leukocytes	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00
Howell-Jolly bodies (% erythrocytes)	0.0 ± 0.0	0.1 ± 0.0	0.0 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.2
Mean cell volume (fL)	49.2 ± 0.1	50.2 ± 0.2**	49.4 ± 0.3	49.2 ± 0.1	49.6 ± 0.2	50.0
Mean cell hemoglobin (pg)	16.0 ± 0.1	16.3 ± 0.1	16.0 ± 0.1	15.9 ± 0.1	16.1 ± 0.1	15.7
Mean cell hemoglobin concentration (g/dL)	32.5 ± 0.1	32.6 ± 0.2	32.4 ± 0.2	32.2 ± 0.2	32.5 ± 0.2	31.7
Platelets (10^3/µL)	924.5 ± 54.2	811.7 ± 21.9*	858.2 ± 7.6	826.0 ± 15.8	815.7 ± 12.4	961.0
Leukocytes (10^3/µL)	3.42 ± 0.25	3.88 ± 0.16	3.12 ± 0.21	3.24 ± 0.19	2.91 ± 0.31	1.50
Segmented neutrophils (10^3/µL)	0.37 ± 0.04	0.55 ± 0.08	0.28 ± 0.03	0.41 ± 0.07	0.48 ± 0.13	0.42
Bands (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00
Lymphocytes (10^3/µL)	3.00 ± 0.24	3.29 ± 0.14	2.80 ± 0.19	2.81 ± 0.14	2.40 ± 0.19	1.05
Monocytes (10^3/µL)	0.03 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.00	0.02
Basophils (10^3/µL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000
Eosinophils (10^3/µL)	0.02 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.03 ± 0.01	0.02

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data. All 200 ppm male mice died before the end of the study; no data are available for this group.
[b] No standard error was calculated or pairwise test performed for this exposure group because only single measurements were available.

APPENDIX G
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

Table G1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 2-Week Inhalation Study of Divinylbenzene-HP G-2
Table G2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 3-Month Inhalation Study of Divinylbenzene-HP G-3
Table G3 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 2-Week Inhalation Study of Divinylbenzene-HP G-4
Table G4 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 3-Month Inhalation Study of Divinylbenzene-HP G-5

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 2-Week Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	5	5	5	5	5	5
Male						
Necropsy body wt	151 ± 5	152 ± 6	155 ± 6	138 ± 2	142 ± 5	135 ± 5*
Heart						
Absolute	0.566 ± 0.018	0.588 ± 0.022	0.612 ± 0.019	0.526 ± 0.005	0.538 ± 0.017	0.532 ± 0.018
Relative	3.748 ± 0.084	3.879 ± 0.044	3.946 ± 0.049*	3.816 ± 0.041	3.804 ± 0.032	3.934 ± 0.041
R. Kidney						
Absolute	0.594 ± 0.029	0.626 ± 0.018	0.662 ± 0.021	0.598 ± 0.011	0.652 ± 0.030	0.638 ± 0.033
Relative	3.923 ± 0.088	4.134 ± 0.045	4.271 ± 0.092**	4.336 ± 0.041**	4.602 ± 0.069**	4.709 ± 0.134**
Liver						
Absolute	6.108 ± 0.283	6.456 ± 0.209	6.726 ± 0.261	5.988 ± 0.178	6.762 ± 0.451	7.096 ± 0.329
Relative	40.358 ± 0.879	42.622 ± 0.676	43.333 ± 0.799	43.415 ± 1.085	47.614 ± 1.684**	52.466 ± 1.619**
Lung						
Absolute	1.122 ± 0.041	1.304 ± 0.063	1.344 ± 0.117	1.238 ± 0.124	1.138 ± 0.061	1.194 ± 0.056
Relative	7.420 ± 0.084	8.627 ± 0.421	8.659 ± 0.688	8.991 ± 0.926	8.038 ± 0.313	8.861 ± 0.463
R. Testis						
Absolute	0.947 ± 0.024	0.949 ± 0.046	0.980 ± 0.039	0.920 ± 0.088	0.932 ± 0.028	0.933 ± 0.040
Relative	6.276 ± 0.105	6.252 ± 0.143	6.310 ± 0.071	6.647 ± 0.548	6.590 ± 0.070	6.894 ± 0.111
Thymus						
Absolute	0.429 ± 0.021	0.468 ± 0.018	0.438 ± 0.014	0.396 ± 0.015	0.395 ± 0.007	0.366 ± 0.018*
Relative	2.837 ± 0.121	3.097 ± 0.143	2.831 ± 0.090	2.876 ± 0.124	2.806 ± 0.114	2.707 ± 0.093
Female						
Necropsy body wt	112 ± 2	115 ± 2	112 ± 3	111 ± 2	106 ± 2	104 ± 2*
Heart						
Absolute	0.454 ± 0.005	0.488 ± 0.014	0.478 ± 0.013	0.472 ± 0.010	0.448 ± 0.006	0.464 ± 0.024
Relative	4.061 ± 0.116	4.252 ± 0.119	4.291 ± 0.160	4.255 ± 0.149	4.218 ± 0.080	4.482 ± 0.237
R. Kidney						
Absolute	0.462 ± 0.008	0.526 ± 0.021*	0.522 ± 0.016*	0.528 ± 0.006**	0.516 ± 0.014*	0.520 ± 0.009*
Relative	4.127 ± 0.070	4.574 ± 0.106**	4.671 ± 0.031**	4.754 ± 0.093**	4.854 ± 0.097**	5.022 ± 0.093**
Liver						
Absolute	4.382 ± 0.055	4.812 ± 0.170*	4.738 ± 0.155*	4.840 ± 0.101*	4.762 ± 0.122*	5.220 ± 0.071**
Relative	39.142 ± 0.303	41.893 ± 1.130**	42.412 ± 0.660**	43.529 ± 0.509**	44.774 ± 0.498**	50.418 ± 0.711**
Lung						
Absolute	0.808 ± 0.016	1.050 ± 0.015*	1.028 ± 0.068*	1.000 ± 0.075	0.974 ± 0.069	0.832 ± 0.029
Relative	7.224 ± 0.202	9.152 ± 0.152*	9.259 ± 0.747*	8.981 ± 0.611	9.158 ± 0.610*	8.049 ± 0.363
Thymus						
Absolute	0.380 ± 0.020	0.388 ± 0.021	0.398 ± 0.022	0.394 ± 0.020	0.365 ± 0.011	0.353 ± 0.010
Relative	3.393 ± 0.171	3.377 ± 0.141	3.558 ± 0.159	3.541 ± 0.135	3.435 ± 0.090	3.412 ± 0.143

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 3-Month Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	302 ± 4	315 ± 7	306 ± 4	300 ± 8	289 ± 9	273 ± 5**
Heart						
Absolute	0.823 ± 0.019	0.869 ± 0.020	0.830 ± 0.011	0.819 ± 0.019	0.839 ± 0.036	0.789 ± 0.013
Relative	2.722 ± 0.043	2.761 ± 0.036	2.715 ± 0.019	2.730 ± 0.025	2.895 ± 0.056**	2.893 ± 0.039**
R. Kidney						
Absolute	0.864 ± 0.018	0.952 ± 0.019*	0.917 ± 0.012	0.923 ± 0.026	0.925 ± 0.033	0.975 ± 0.018**
Relative	2.856 ± 0.035	3.026 ± 0.034**	3.001 ± 0.035**	3.074 ± 0.024**	3.198 ± 0.056**	3.570 ± 0.029**
Liver						
Absolute	9.121 ± 0.197	10.127 ± 0.234*	9.773 ± 0.186	9.601 ± 0.341	9.401 ± 0.297	9.432 ± 0.178
Relative	30.145 ± 0.379	32.177 ± 0.471**	31.981 ± 0.556**	31.914 ± 0.378**	32.506 ± 0.270**	34.557 ± 0.544**
Lung						
Absolute	1.582 ± 0.038	1.594 ± 0.045	1.496 ± 0.025	1.572 ± 0.043	1.497 ± 0.038	1.432 ± 0.029**
Relative	5.236 ± 0.124	5.061 ± 0.077	4.897 ± 0.088	5.247 ± 0.113	5.194 ± 0.106	5.245 ± 0.65
R. Testis						
Absolute	1.317 ± 0.016	1.373 ± 0.017	1.309 ± 0.032	1.325 ± 0.024	1.325 ± 0.043	1.278 ± 0.021
Relative	4.362 ± 0.077	4.369 ± 0.057	4.279 ± 0.066	4.427 ± 0.072	4.590 ± 0.107*	4.682 ± 0.048**
Thymus						
Absolute	0.285 ± 0.013	0.306 ± 0.011	0.300 ± 0.013	0.276 ± 0.011	0.269 ± 0.013	0.260 ± 0.012
Relative	0.944 ± 0.049	0.975 ± 0.041	0.983 ± 0.044	0.921 ± 0.034	0.935 ± 0.046	0.955 ± 0.053
Female						
Necropsy body wt	182 ± 3	185 ± 4	196 ± 4	183 ± 3	177 ± 5	178 ± 4
Heart						
Absolute	0.596 ± 0.010	0.603 ± 0.011	0.619 ± 0.010	0.582 ± 0.011	0.596 ± 0.014	0.594 ± 0.012
Relative	3.269 ± 0.034	3.272 ± 0.057	3.164 ± 0.034	3.177 ± 0.028	3.388 ± 0.086	3.335 ± 0.045
R. Kidney						
Absolute	0.599 ± 0.013	0.609 ± 0.012	0.624 ± 0.011	0.596 ± 0.015	0.596 ± 0.018	0.656 ± 0.016*
Relative	3.285 ± 0.036	3.300 ± 0.035	3.191 ± 0.038	3.253 ± 0.064	3.378 ± 0.064	3.680 ± 0.052**
Liver						
Absolute	5.502 ± 0.150	5.524 ± 0.151	5.920 ± 0.188	5.527 ± 0.173	5.421 ± 0.177	6.506 ± 0.221**
Relative	30.189 ± 0.654	29.896 ± 0.425	30.233 ± 0.656	30.105 ± 0.554	30.726 ± 0.697	36.419 ± 0.657**
Lung						
Absolute	1.128 ± 0.035	1.149 ± 0.027	1.136 ± 0.029	1.096 ± 0.020	1.055 ± 0.025	1.116 ± 0.031
Relative	6.182 ± 0.119	6.227 ± 0.123	5.810 ± 0.123	5.990 ± 0.122	6.007 ± 0.190	6.260 ± 0.137
Thymus						
Absolute	0.239 ± 0.009	0.255 ± 0.006	0.262 ± 0.009	0.247 ± 0.010	0.256 ± 0.016	0.215 ± 0.008
Relative	1.309 ± 0.034	1.384 ± 0.041	1.341 ± 0.045	1.347 ± 0.042	1.450 ± 0.082	1.207 ± 0.040

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

Table G3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 2-Week Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	25 ppm	50 ppm	100 ppm	200 ppm	400 ppm
n	5	5	5	5	3	0
Male						
Necropsy body wt	28.7 ± 0.2	26.5 ± 0.6*	26.2 ± 0.8*	25.7 ± 0.5**	23.3 ± 1.35 **	
Heart						
Absolute	0.134 ± 0.004	0.114 ± 0.004	0.114 ± 0.002	0.138 ± 0.009	0.130 ± 0.015	
Relative	4.673 ± 0.114	4.312 ± 0.144	4.356 ± 0.087	5.374 ± 0.307	5.548 ± 0.484	
R. Kidney						
Absolute	0.250 ± 0.005	0.228 ± 0.015	0.236 ± 0.008	0.226 ± 0.002	0.230 ± 0.000	
Relative	8.720 ± 0.150	8.584 ± 0.376	9.004 ± 0.179	8.819 ± 0.182	9.912 ± 0.510*	
Liver						
Absolute	1.394 ± 0.022	1.342 ± 0.045	1.252 ± 0.043	1.366 ± 0.040	1.537 ± 0.041	
Relative	48.635 ± 0.646	50.716 ± 1.202	47.751 ± 0.581	53.232 ± 1.174**	66.062 ± 2.076**	
Lung						
Absolute	0.200 ± 0.003	0.206 ± 0.014	0.190 ± 0.009	0.200 ± 0.007	0.177 ± 0.018	
Relative	6.978 ± 0.093	7.764 ± 0.382	7.249 ± 0.284	7.786 ± 0.152	7.536 ± 0.354	
R. Testis						
Absolute	0.100 ± 0.002	0.091 ± 0.004	0.089 ± 0.007	0.092 ± 0.006	0.090 ± 0.003	
Relative	3.498 ± 0.082	3.469 ± 0.207	3.366 ± 0.173	3.570 ± 0.229	3.872 ± 0.165	
Thymus						
Absolute	0.060 ± 0.003	0.044 ± 0.005*	0.044 ± 0.005*	0.039 ± 0.006**	0.019 ± 0.003**	
Relative	2.094 ± 0.090	1.672 ± 0.197	1.701 ± 0.191	1.498 ± 0.225*	0.827 ± 0.135**	
Female						
Necropsy body wt	20.9 ± 0.8	22.6 ± 0.3	21.8 ± 0.7	21.6 ± 0.5	20.2 ± 0.9	
Heart						
Absolute	0.106 ± 0.002	0.108 ± 0.004	0.102 ± 0.002	0.108 ± 0.004	0.103 ± 0.009	
Relative	5.090 ± 0.155	4.767 ± 0.122	4.703 ± 0.147	4.996 ± 0.131	5.089 ± 0.205	
R. Kidney						
Absolute	0.144 ± 0.004	0.184 ± 0.007**	0.168 ± 0.002**	0.164 ± 0.004*	0.183 ± 0.003**	
Relative	6.905 ± 0.156	8.118 ± 0.202**	7.741 ± 0.166	7.602 ± 0.259	9.109 ± 0.547**	
Liver						
Absolute	0.944 ± 0.050	1.140 ± 0.030*	1.084 ± 0.073	1.078 ± 0.020	1.277 ± 0.061**	
Relative	45.086 ± 1.045	50.365 ± 1.301*	49.597 ± 2.057*	49.964 ± 1.436*	63.079 ± 0.207**	
Lung						
Absolute	0.168 ± 0.005[b]	0.202 ± 0.010**	0.186 ± 0.004	0.178 ± 0.002	0.153 ± 0.003	
Relative	7.796 ± 0.374[b]	8.910 ± 0.358	8.571 ± 0.241	8.248 ± 0.184	7.620 ± 0.483	
Thymus						
Absolute	0.053 ± 0.008	0.067 ± 0.003	0.052 ± 0.004	0.060 ± 0.004	0.032 ± 0.005	
Relative	2.507 ± 0.373	2.964 ± 0.154	2.401 ± 0.149	2.799 ± 0.182	1.583 ± 0.290	

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error). All 400 ppm male and female mice died before the end of the study; no data are available for these groups.
[b] n=4

Table G4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 3-Month Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	12.5 ppm	25 ppm	50 ppm	100 ppm	200 ppm
Male						
n	10	10	10	10	10	0
Necropsy body wt	36.8 ± 0.5	37.0 ± 0.7	33.2 ± 0.8**	31.8 ± 0.8**	31.3 ± 0.4**	
Heart						
Absolute	0.156 ± 0.002	0.161 ± 0.003	0.145 ± 0.005*	0.135 ± 0.002**	0.134 ± 0.003**	
Relative	4.247 ± 0.053	4.364 ± 0.067	4.367 ± 0.102	4.268 ± 0.097	4.295 ± 0.115	
R. Kidney						
Absolute	0.312 ± 0.008	0.306 ± 0.008	0.277 ± 0.011**	0.261 ± 0.005**	0.247 ± 0.004**	
Relative	8.481 ± 0.159	8.279 ± 0.110	8.329 ± 0.197	8.236 ± 0.135	7.911 ± 0.153*	
Liver						
Absolute	1.497 ± 0.029	1.522 ± 0.039	1.307 ± 0.052**	1.247 ± 0.021**	1.259 ± 0.024**	
Relative	40.723 ± 0.670	41.155 ± 0.387	39.314 ± 0.917	39.362 ± 0.545	40.276 ± 0.482	
Lung						
Absolute	0.235 ± 0.005	0.255 ± 0.008	0.238 ± 0.009	0.231 ± 0.009	0.219 ± 0.007	
Relative	6.398 ± 0.136	6.907 ± 0.207	7.164 ± 0.190*	7.282 ± 0.224**	7.003 ± 0.172	
R. Testis						
Absolute	0.117 ± 0.002	0.124 ± 0.002	0.115 ± 0.003	0.117 ± 0.003	0.116 ± 0.001	
Relative	3.191 ± 0.037	3.352 ± 0.052	3.478 ± 0.104**	3.691 ± 0.067**	3.731 ± 0.065**	
Thymus						
Absolute	0.038 ± 0.002	0.039 ± 0.002	0.037 ± 0.003	0.035 ± 0.001	0.036 ± 0.003	
Relative	1.043 ± 0.043	1.060 ± 0.043	1.118 ± 0.084	1.099 ± 0.046	1.166 ± 0.098	
Female						
n	10	10	10	10	10	1[b]
Necropsy body wt	31.1 ± 0.8	31.9 ± 1.2	28.5 ± 0.4**	28.3 ± 0.4**	28.1 ± 0.3**	26.8
Heart						
Absolute	0.140 ± 0.003	0.141 ± 0.005	0.129 ± 0.003*	0.126 ± 0.004**	0.120 ± 0.003**	0.110
Relative	4.520 ± 0.123	4.446 ± 0.160	4.537 ± 0.095	4.447 ± 0.102	4.277 ± 0.106	4.104
R. Kidney						
Absolute	0.197 ± 0.005	0.208 ± 0.004	0.191 ± 0.003	0.190 ± 0.004	0.196 ± 0.004	0.200
Relative	6.348 ± 0.168	6.563 ± 0.145	6.729 ± 0.157	6.720 ± 0.137	6.982 ± 0.135**	7.463
Liver						
Absolute	1.415 ± 0.052	1.463 ± 0.069	1.323 ± 0.023	1.204 ± 0.022**	1.177 ± 0.026**	1.250
Relative	45.466 ± 1.128	45.772 ± 0.834	46.522 ± 0.702	42.534 ± 0.529*	41.907 ± 0.841**	46.642
Lung						
Absolute	0.233 ± 0.006	0.266 ± 0.009	0.246 ± 0.005	0.227 ± 0.005	0.218 ± 0.004	0.210
Relative	7.533 ± 0.272	8.382 ± 0.258*	8.651 ± 0.181**	8.012 ± 0.072	7.771 ± 0.165	7.836
Thymus						
Absolute	0.045 ± 0.002	0.047 ± 0.002	0.045 ± 0.002	0.036 ± 0.004*	0.038 ± 0.001*	0.026
Relative	1.459 ± 0.077	1.477 ± 0.052	1.585 ± 0.071	1.273 ± 0.125	1.354 ± 0.036	0.970

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] No standard error was calculated or pairwise test performed for this exposure group because only single measurements were available.

APPENDIX H
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

Table H1	**Summary of Reproductive Tissue Evaluations for Male Rats in the 3-Month Inhalation Study of Divinylbenzene-HP**	**H-2**
Table H2	**Estrous Cycle Characterization for Female Rats in the 3-Month Inhalation Study of Divinylbenzene-HP**	**H-2**
Table H3	**Summary of Reproductive Tissue Evaluations for Male Mice in the 3-Month Inhalation Study of Divinylbenzene-HP**	**H-3**
Table H4	**Estrous Cycle Characterization for Female Mice in the 3-Month Inhalation Study of Divinylbenzene-HP**	**H-3**

Table H1
Summary of Reproductive Tissue Evaluations for Male Rats in the 3-Month Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	100 ppm	200 ppm	400 ppm
n	10	10	10	10
Weights (g)				
Necropsy body wt	302 ± 4	300 ± 8	289 ± 9	273 ± 5**
L. Cauda epididymis	0.1644 ± 0.0042	0.1576 ± 0.0086	0.1539 ± 0.0068	0.1515 ± 0.0039
L. Epididymis	0.4489 ± 0.0074	0.4364 ± 0.0125	0.4224 ± 0.0157	0.4187 ± 0.0109
L. Testis	1.3959 ± 0.0088	1.3976 ± 0.0321	1.3839 ± 0.0406	1.3234 ± 0.0267
Spermatid measurement				
Spermatid heads (10^7/g testis)	12.99 ± 0.58	13.42 ± 0.66	12.83 ± 0.66	13.31 ± 0.90
Spermatid heads (10^7/testis)	16.99 ± 0.72	17.66 ± 1.03	16.65 ± 0.90	16.85 ± 1.24
Epididymal spermatozoal measurements				
Sperm (10^6/g cauda epididymis)	787 ± 32	786 ± 51	818 ± 40	781 ± 37
Sperm (10^6/cauda epididymis)	26 ± 1	24 ± 1	25 ± 2	24 ± 1
Sperm motility (%)	77.24 ± 2.79	75.60 ± 3.06	79.21 ± 2.99	74.43 ± 1.76

** Significantly different ($P \leq 0.01$) from the chamber control group by Williams' test
[a] Data are presented as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test (tissue weights) or Dunn's test (spermatid and epididymal spermatozoal measurements).

Table H2
Estrous Cycle Characterization for Female Rats in the 3-Month Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	100 ppm	200 ppm	400 ppm
n	10	10	10	10
Necropsy body wt (g)	182 ± 3	183 ± 3	177 ± 5	178 ± 4
Estrous cycle length (days)	4.85 ± 0.08	4.75 ± 0.13	4.90 ± 0.07	4.70 ± 0.15
Estrous stages (% of cycle)				
Diestrus	38.3	42.5	41.7	46.7
Proestrus	20.8	18.3	17.5	13.3
Estrus	20.8	22.5	23.3	23.3
Metestrus	20.0	16.7	16.7	16.7
Uncertain diagnoses	0.0	0.0	0.8	0.0

[a] Necropsy body weights and estrous cycle length data are presented as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test (body weight) or Dunn's test (estrous cycle length). By multivariate analysis of variance, exposed females do not differ significantly from the chamber control females in the relative length of time spent in the estrous stages.

Table H3
Summary of Reproductive Tissue Evaluations for Male Mice in the 3-Month Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	25 ppm	50 ppm	100 ppm
n	10	10	10	10
Weights (g)				
Necropsy body wt	36.8 ± 0.5	33.2 ± 0.8**	31.8 ± 0.8**	31.3 ± 0.4**
L. Cauda epididymis	0.0191 ± 0.0012	0.0205 ± 0.0005	0.0194 ± 0.0008	0.0193 ± 0.0012
L. Epididymis	0.0577 ± 0.0054	0.0544 ± 0.0021	0.0511 ± 0.0018	0.0536 ± 0.0023
L. Testis	0.1167 ± 0.0036	0.1140 ± 0.0027	0.1146 ± 0.0022	0.1178 ± 0.0028
Spermatid measurements				
Spermatid heads (10^7/g testis)	23.92 ± 0.66	25.22 ± 1.24	21.65 ± 0.88[b]	24.07 ± 1.19[b]
Spermatid heads (10^7/testis)	2.51 ± 0.07	2.62 ± 0.15	2.29 ± 0.08	2.50 ± 0.11
Epididymal spermatozoal measurements				
Sperm heads (10^6/g cauda epididymis)	1,157 ± 98	1,134 ± 66	1,173 ± 73	1,315 ± 95
Sperm heads (10^6/cauda epididymis)	22 ± 2	23 ± 1	23 ± 1	24 ± 1
Sperm motility (%)	64.16 ± 1.49[b]	64.98 ± 1.99	65.27 ± 1.13	59.52 ± 2.53

** Significantly different ($P \le 0.01$) from the chamber control group by Williams' test
a Data are presented as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test (tissue weights) or Dunn's test (spermatid and epididymal spermatozoal measurements).
b n=9

Table H4
Estrous Cycle Characterization for Female Mice in the 3-Month Inhalation Study of Divinylbenzene-HP[a]

	Chamber Control	25 ppm	50 ppm	100 ppm
n	10	10	10	10
Necropys body wt (g)	31.1 ± 0.8	28.5 ± 0.4**	28.3 ± 0.4**	28.1 ± 0.3**
Estrous cycle length (days)	4.45 ± 0.40	4.22 ± 0.21	4.45 ± 0.09	4.70 ± 0.37
Estrous stages (% of cycle)				
Diestrus	29.2	28.3	30.0	32.5
Proestrus	9.2	15.0	13.3	10.8
Estrus	38.3	33.3	33.3	34.2
Metestrus	23.3	23.3	23.3	22.5

** Significantly different ($P \le 0.01$) from the chamber control group by Williams' test
a Necropsy body weights and estrous cycle length data are presented as mean ± standard error. Differences from the chamber control group for estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, exposed females do not differ significantly from the chamber control females in the relative length of time spent in the estrous stages.

APPENDIX I
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

Procurement and Characterization of Divinylbenzene-HP I-2
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CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF DIVINYLBENZENE-HP

Divinylbenzene-HP (80% divinylbenzene with 20% ethylvinylbenzene) was obtained from Dow Chemical Company (Midland, MI) in two lots (LJ31012V18 and ND13012V23). Lot LJ31012V18 was used in the 2-week and 3-month studies, and lot ND13012V23 was used during the 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC); Chemir/Polytech Laboratories, Inc. (Maryland Heights, MO); and the study laboratory, Battelle Northwest Operations (Richland, WA). Reports on analyses performed in support of the divinylbenzene-HP studies are on file at the National Institute of Environmental Health Sciences.

Lots LJ31012V18 and ND13012V23, pale, straw-colored liquids with a hydrocarbon odor, were identified as divinylbenzene-HP by the analytical chemistry laboratory using infrared (IR) and proton nuclear magnetic resonance (NMR) spectroscopy and gas chromatography/mass spectrometry (GC/MS) by systems A and B, respectively; by Chemir/Polytech Laboratories, Inc., using IR spectroscopy; and by the study laboratory using GC/MS by systems C and D, respectively (Table I1). The IR (Aldrich, 1997; FSCT, 1991), proton NMR (RTI, 1999), and GC/MS (NIST, 1994, 1995a,b) spectra were consistent with reference and literature spectra of divinylbenzene-HP. The IR, proton NMR, and mass spectra are presented in Figures I1, I2, and I3, respectively.

The purity of lot LJ31012V18 was determined by the analytical chemistry laboratory using GC with flame ionization detection (FID) by system E and by the study laboratory using GC/FID by system F. The purity of lot ND13012V23 was determined by the analytical chemistry laboratory using GC/FID by system G and by the study laboratory using GC/FID by systems H and I. For both lots, elemental analyses and moisture analyses by Karl Fischer titration were performed by Chemir/Polytech Laboratories, Inc., and concentrations of 4-*tert*-butylcatechol added as a polymerization inhibitor were measured by the analytical chemistry laboratory and the study laboratory using GC, high-performance liquid chromatography (HPLC), or ultraviolet/visible (UV/Vis) spectroscopy. Polymer concentrations were measured in both lots by the study laboratory using a UV/Vis turbidity assay.

For lot LJ31012V18, elemental analyses for carbon and hydrogen were in agreement with the theoretical values for divinylbenzene-HP (80% divinylbenzene with 20% ethylvinylbenzene). Karl Fischer titration indicated a moisture content of 87 ± 5 ppm. Polymer content and 4-*tert*-butylcatechol concentrations were well within the specifications of < 20 ppm and > 600 ppm, respectively. GC/FID by system E and GC/MS by system A detected four major peaks that were identified as the *meta*- and *para*-isomers of divinylbenzene and ethylvinylbenzene; the percent total area of the divinylbenzene isomers was 79.3%. GC/FID by system F and GC/MS by system C detected four major peaks and two minor impurity peaks; the minor peaks had areas of approximately 0.1% of the total peak area. The percent total area of the divinylbenzene isomers was 80.2%. Measured as the sum of the *meta*- and *para*-isomers of divinylbenzene, the overall purity of lot LJ31012V18 was determined to be approximately 80%.

For lot ND13012V23, elemental analyses for carbon, hydrogen, nitrogen, and sulfur were in agreement with the theoretical values for divinylbenzene-HP. Karl Fischer titration indicated a moisture content of approximately 200 ppm. Polymer content and 4-*tert*-butylcatechol concentrations were well within the specifications of < 20 ppm and > 600 ppm, respectively. GC/FID by system G and GC/MS by system B detected four major peaks that were identified as the *meta*- and *para*-isomers of divinylbenzene and ethylvinylbenzene; the percent total area of the divinylbenzene isomers was 81.2%. GC/FID by system H indicated a purity exceeding 99.9% relative to a reference standard. GC/FID by system I and GC/MS by system D detected four major peaks and one minor impurity peak having an area percent of 0.13%; the retention time of this minor peak matched that of naphthalene. The percent total area of the divinylbenzene isomers was 81%. Measured as the sum of the *meta*- and *para*-isomers of divinylbenzene, the overall purity of lot ND13012V23 was determined to be approximately 81%.

To ensure stability, the bulk chemical was stored in its original shipping containers, 5-gallon metal pails, at approximately –20° C. Periodic reanalyses of area percent purity and purity relative to a reference standard stored at –70° C were conducted by the study laboratory during the 3-month and 2-year studies with GC/FID by systems F and I. Periodic reanalyses of polymer and 4-*tert*-butylcatechol content were conducted by the study laboratory using a GC/FID system similar to system L and HPLC analysis during the 3-month and 2-year studies, respectively. The HPLC analysis used a Waters Nova-Pak® C18 column (300 mm × 3.9 mm, 4 µm particle size; Waters Corp., Milford, MA) and a mobile phase of 1% acetic acid in methanol (A) and 1% acetic acid in water (B). The mobile phase gradient was 0% A: 100% B for 2 minutes, changed to 100% A: 0% B over the next 11 minutes, held for 4 minutes, and then rapidly reversed to 0% A: 100% B in 0.1 minutes. The flow rate was 0.75 mL/minute, and detection was at 270 and 309 nm. No degradation of the bulk chemical was detected, and polymer and 4-*tert*-butylcatechol concentrations remained within the specifications of < 20 ppm and > 600 ppm, respectively.

Vapor Generation and Exposure System

A diagram of the vapor generation and delivery system used in the studies is shown in Figure I4. Preheated divinylbenzene-HP was pumped onto glass beads in a heated glass column where it was vaporized. Heated air flowed through the column and carried the vapor out of the generator. Generator output was controlled by the delivery rate of the chemical metering pump.

Because the vapor leaving the generator was above room temperature, it was transported to the exposure room at an elevated temperature to prevent condensation. In the exposure room, the vapor was mixed with additional heated air before entering a short vapor distribution manifold. Concentration in the manifold was determined by the chemical pump rate, generator air flow rate, and dilution air flow rate. The exposure operator monitored all three components. The pressure in the distribution manifold was kept fixed to ensure constant flows through the manifold and into the chambers.

An electronically actuated metering valve controlled the flow to each chamber; a pneumatically operated chamber exposure shutoff valve in line with the metering valve stopped flow to the chamber. In addition, for the chambers used for the two lowest exposure concentrations in each study, a compressed air vacuum pump was attached to the chamber end of the delivery line and used for fine control of the vapor delivery rate. Until the generation system was stable and exposures were ready to proceed, all chamber exposure valves were closed and vapor was directed to the exposure chamber exhaust. When the exposure started, the chamber exposure valves were opened to allow the vapor to flow through the metering valves and then through temperature-controlled delivery lines to each exposure chamber. The vapor was then injected into the chamber inlet duct where it was further diluted with conditioned chamber air to achieve the desired exposure concentration.

The study laboratory designed the inhalation exposure chamber (H-2000; Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chamber with the catch pans in place. The total active mixing volume of each chamber was 1.7 m^3. A condensation particle counter (Model 3022A, TSI, Inc., St. Paul, MN) was used to count the particles in the rooms (2-week and 3-month studies) and all exposure chambers (all studies) before the start of generation and during generation to determine whether divinylbenzene-HP vapor, and not aerosol, was produced. Low levels of particulate material above that typically observed as background in control and treated chambers were detected in exposure chambers during the 3-month studies. However, there was no consistent difference between measurements made before and during exposure and no trend toward increased particulate levels with increased concentration except for the 400 ppm chamber in the 13-week study, which showed slightly higher particulate levels compared to other chambers. In the 3-month studies, there was no airflow in the heated delivery lines between exposures. During the 2-year studies, a continuous flow of compressed air through the heated delivery lines was continued between exposures as well as during the exposures to purge the system of any divinylbenzene that might subsequently form aerosols or polymerize. Measurements before and during 2-year study exposure periods did not show any significant particulate levels above background, even in the 400 ppm chambers.

Vapor Concentration Monitoring

Summaries of the chamber vapor concentrations are given in Tables I2 through I4. Concentrations of divinylbenzene-HP in the exposure chambers were monitored by an on-line gas chromatograph equipped with FID using system J (2-week and 3-month studies) or system K (2-year studies). Samples were drawn from each exposure chamber approximately every 36 minutes using Hastelloy-C gas-sampling and stream-select valves (Valco Instruments Co., Houston, TX) in a separate, heated valve oven. The sample lines were made from 1/16-inch Teflon® tubing and were connected to the exposure chamber relative humidity sampling lines at a location close to the gas chromatograph.

The on-line gas chromatograph was checked throughout the day for instrument drift by analyzing an on-line standard of 1,4-diethylbenzene in nitrogen supplied by a diffusion tube standard generator (Kin-Tek, Model 491, Precision Calibration Systems, La Marque, TX). The on-line gas chromatograph was calibrated during routine exposure periods by a comparison of chamber concentration data to data from grab samples that were collected with charcoal sampling tubes (ORBO™-101, Supelco, Bellefonte, PA), extracted with toluene containing 1-phenylhexane as an internal standard, and analyzed by an off-line gas chromatograph using system L with FID. The volumes of gas were sampled at a constant flow rate ensured by a calibrated critical orifice. The off-line gas chromatograph was calibrated with gravimetrically prepared standards of divinylbenzene-HP and the internal standard (1-phenylhexane) in toluene.

Chamber Atmosphere Characterization

Buildup and decay rates for chamber vapor concentrations were determined with animals present in the chambers. At a chamber airflow rate of 15 air changes per hour, the theoretical value for the time to achieve 90% of the target concentration after the beginning of vapor generation (T_{90}) and the time for the chamber concentration to decay to 10% of the target concentration after vapor generation was terminated (T_{10}) was approximately 12.5 minutes. For rats and mice in 2-week studies, T_{90} values ranged from 11 to 15 minutes; T_{10} values ranged from 12 to 16 minutes. For rats in the 3-month studies, T_{90} values ranged from 12 to 14 minutes; T_{10} values ranged from 15 to 16 minutes. For mice in the 3-month studies, T_{90} values ranged from 11 to 14 minutes; T_{10} values ranged from 10 to 16 minutes. For rats in the 2-year studies, T_{90} values ranged from 14 to 16 minutes; T_{10} values ranged from 23 to 27 minutes. For mice in the 2-year studies, T_{90} values ranged from 12 to 14 minutes; T_{10} values ranged from 16 to 26 minutes. A T_{90} value of 12 minutes was selected for all studies.

Chamber concentration uniformity was evaluated before the 2-year study without animals and during all studies. It was also measured once during the 2-week studies, once during the 3-month studies, and approximately every 3 months during the 2-year studies. The vapor concentration was measured using the on-line gas chromatograph with FID (analysis by system J for the 2-week and 3-week studies and by system K for the 2-year studies) with the automatic 12-port sample valve disabled to allow continuous monitoring from a single input line. Samples were collected from twelve positions in each chamber. Chamber concentration uniformity was maintained throughout the studies.

The persistence of divinylbenzene-HP in the chambers with animals present after vapor delivery ended was determined by monitoring the concentration after shutoff of test article to the 400 ppm chambers (2-week rat and mouse studies and 3-month and 2-year rat studies) and 100 ppm chambers (2-year mouse study). In the 2-week studies, the concentration decreased to 1% of the target concentration within 164 minutes. In the 3-month study, the concentration decreased to 1% of the target concentration within 144 minutes. In the 2-year studies, the concentration decreased to 1% of the target concentration within 202 (rats) or 403 (mice) minutes.

Stability studies of the divinylbenzene-HP in the generation and delivery system were performed. Samples of the test atmosphere from the distribution manifold and the low and high exposure concentration chambers (25 and 400 ppm in the 2-week studies, 12.5 and 400 ppm in the 3-month studies, and 100 and 400 ppm (rats) and 10 and 100 ppm (mice) in the 2-year studies) were collected with ORBO^{TM}-101 charcoal sampling tubes during the first and last hours of generation with animals present in the chambers. The samples were extracted with methylene chloride and analyzed with GC/FID by system F or a similar system. Resolved peaks corresponded to those identified in a divinylbenzene-HP reference chemical and the initial bulk purity assays. No evidence of degradation was detected, and no impurities were detected that were not present in the bulk material. The stability of divinylbenzene-HP in the generator reservoir was monitored during the 2-week studies and during prestart testing for the 2-year studies. Generator reservoir samples were collected twice during each of these studies and were analyzed with GC/FID by system F or a similar system. No evidence of degradation of the test chemical in the generator reservoir was found. The results indicated that divinylbenzene-HP would remain stable for the period of time the test chemical would be stored in the generator reservoir. All measurements of polymer and 4-*tert*-butylcatechol concentrations in exposure chamber and generator reservoir samples were within the required specifications of < 20 ppm and > 600 ppm, respectively.

Table I1
Gas Chromatography Systems Used in the Inhalation Studies of Divinylbenzene-HP[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A			
Mass spectrometry	DB-5MS, 28.7 m × 0.25 mm, 0.25-µm film (J&W Scientific, Folsom, CA)	Helium at 1.2 mL/minute	75° C for 15 minutes, then 20° C/minute to 300° C, held for 5 minutes
System B			
Mass spectrometry	DB-5MS, 30 m × 0.25 mm, 0.25-µm film (J&W Scientific)	Helium at 1.0 mL/minute	75° C for 15 minutes, then 10° C/minute to 250° C, held for 7.5 minutes
System C			
Mass spectrometry	Rtx-5, 30 m × 0.25 mm, 0.5-µm film (Restek) Bellefonte, PA)	Helium at 3 psi	35° C for 2 minutes, then 2° C/minute to 100° C, held for 1 minute, then 50° C/minute to 200° C, held for 1 minute
System D			
Mass spectrometry	DB-5, 30 m × 0.25 mm, 0.25-µm film (J&W Scientific)	Helium at 10 psi	35° C for 1 minute, then 8° C/minute to 180° C, held for 1 minute
System E			
Flame ionization	DB-5MS, 30 m × 0.32 mm, 0.5-µm film (J&W Scientific)	Helium at 1.1 mL/minute	100° C for 15 minutes, then 20° C/minute to 300° C, held for 5 minutes
System F			
Flame ionization	Rtx-5, 30 m × 0.25 mm, 1.0-µm film (Restek)	Helium at 24 psi	35° C for 1 minute, then 2° C/minute to 120° C, held for 2 minutes, then 10° C/minute to 225° C
System G			
Flame ionization	DB-5, 30 m × 0.25 mm, 0.25-µm film (J&W Scientific)	Helium at 1.0 mL/minute	75° C for 15 minutes, then 10° C/minute to 250° C, held for 7.5 minutes
System H			
Flame ionization	Rtx-5, 30 m × 0.25 mm, 1.0-µm film (Restek)	Helium at 24 psi	40° C for 3 minute, then 8° C/minute to 180° C , held for 1 minute
System I			
Flame ionization	Rtx-5, 30 m × 0.25 mm, 1.0-µm film (Restek)	Helium at 24 psi	35° C for 1 minute, then 3° C/minute to 120°C, then 10° C/minute to 225°C, held for 1 minute
System J			
Flame ionization	DB-5, 30 m × 0.53 mm, 1.5-µm film (J&W Scientific)	Nitrogen at 25 mL/minute	140° C isocratic
System K			
Flame ionization	DB-5, 15 m × 0.53 mm, 0.5-µm film (J&W Scientific)	Nitrogen at 8 psi	110° C f isocratic
System L			
Flame ionization	DB-5, 30 m × 0.53 mm, 1.5-µm film (J&W Scientific)	Helium at 6 psi	90° C for 1 minute, then 16° C/minute to 210° C, then 25° C/minute to 280° C, held for 1 minute

[a] All gas chromatographs were manufactured by Hewlett-Packard (Palo Alto, CA).

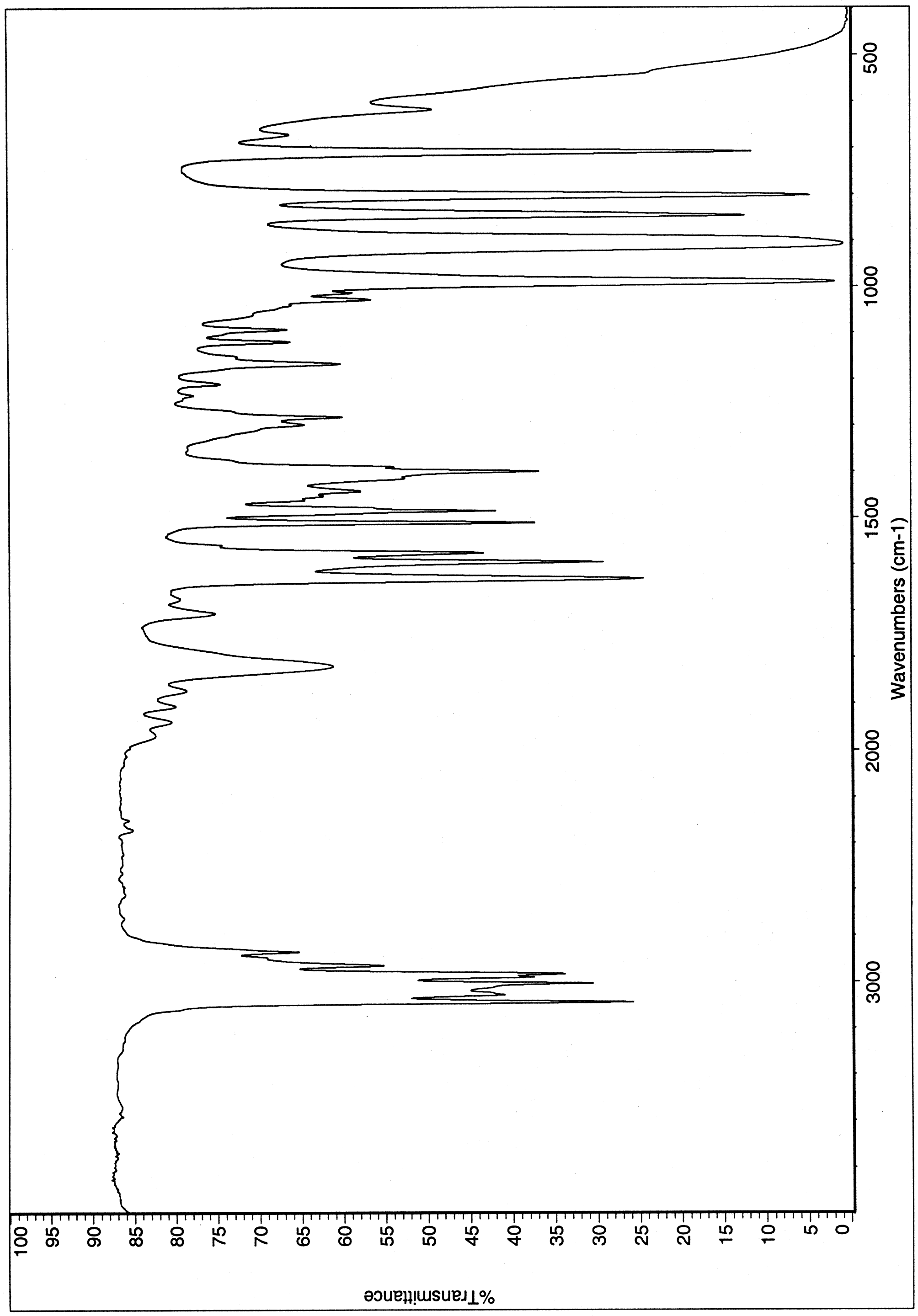

FIGURE I1
Infrared Absorption Spectrum of Divinylbenzene-HP

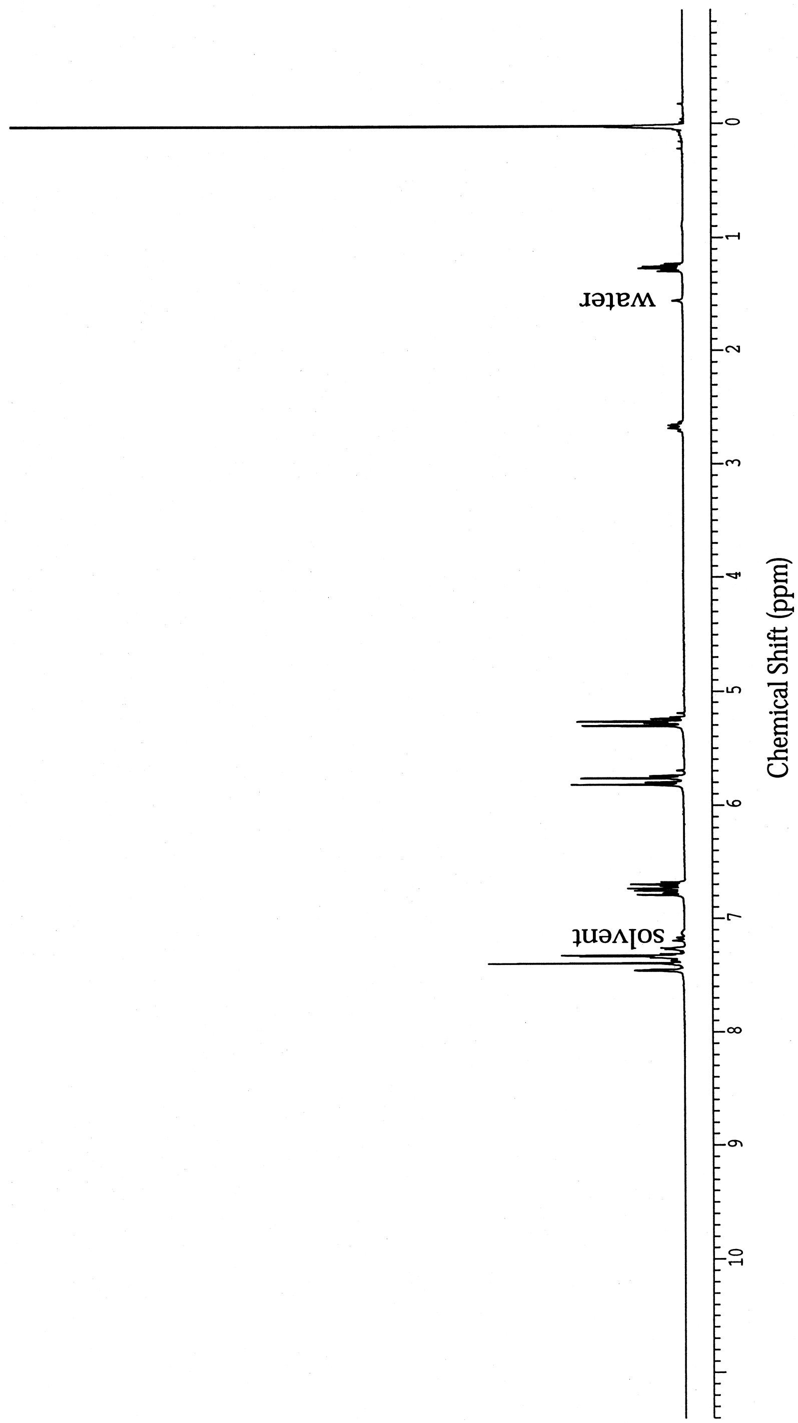

FIGURE I2
Proton Nuclear Magnetic Resonance Spectrum of Divinylbenzene-HP

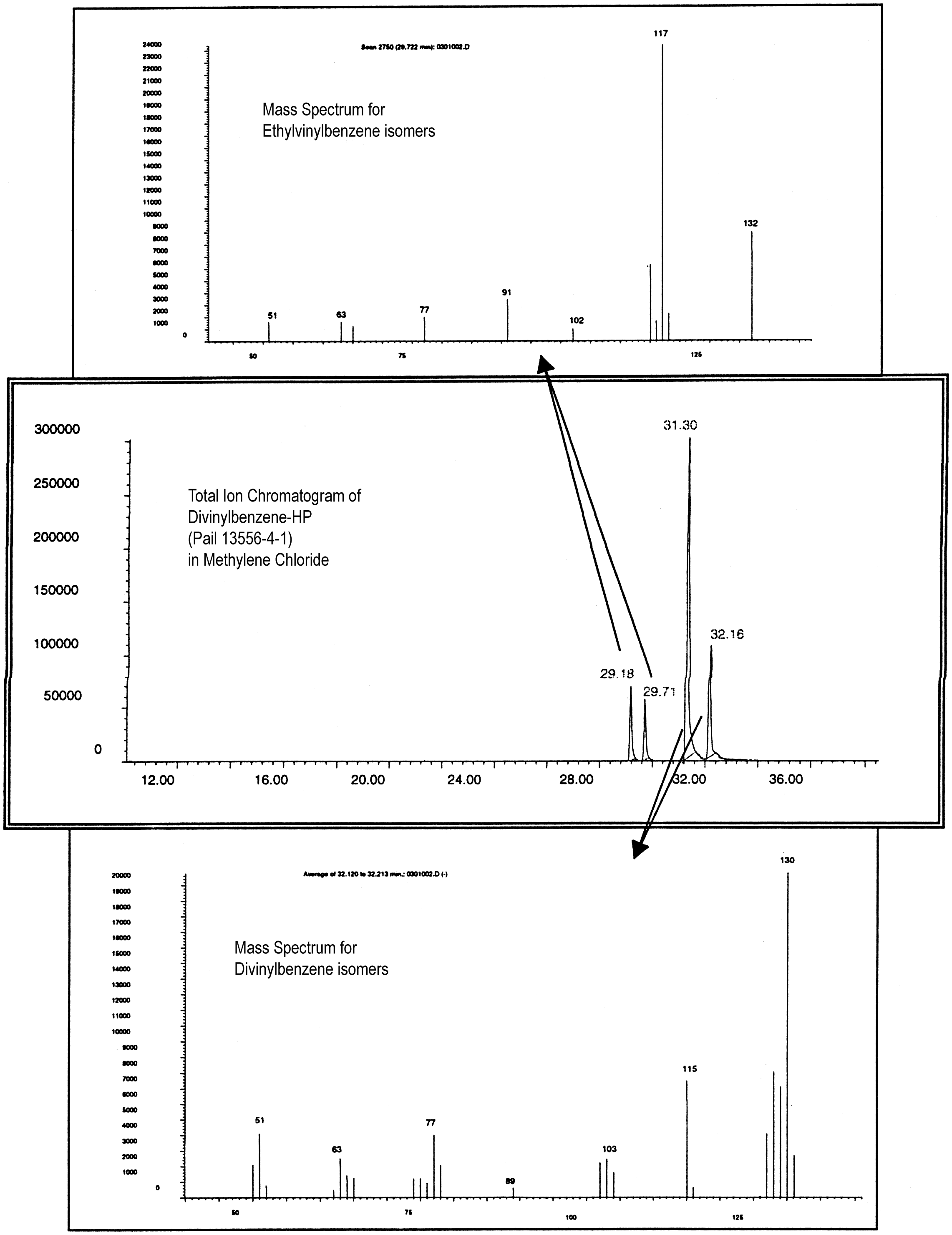

FIGURE I3
Gas Chromatogram/Mass Spectra of Divinylbenzene-HP

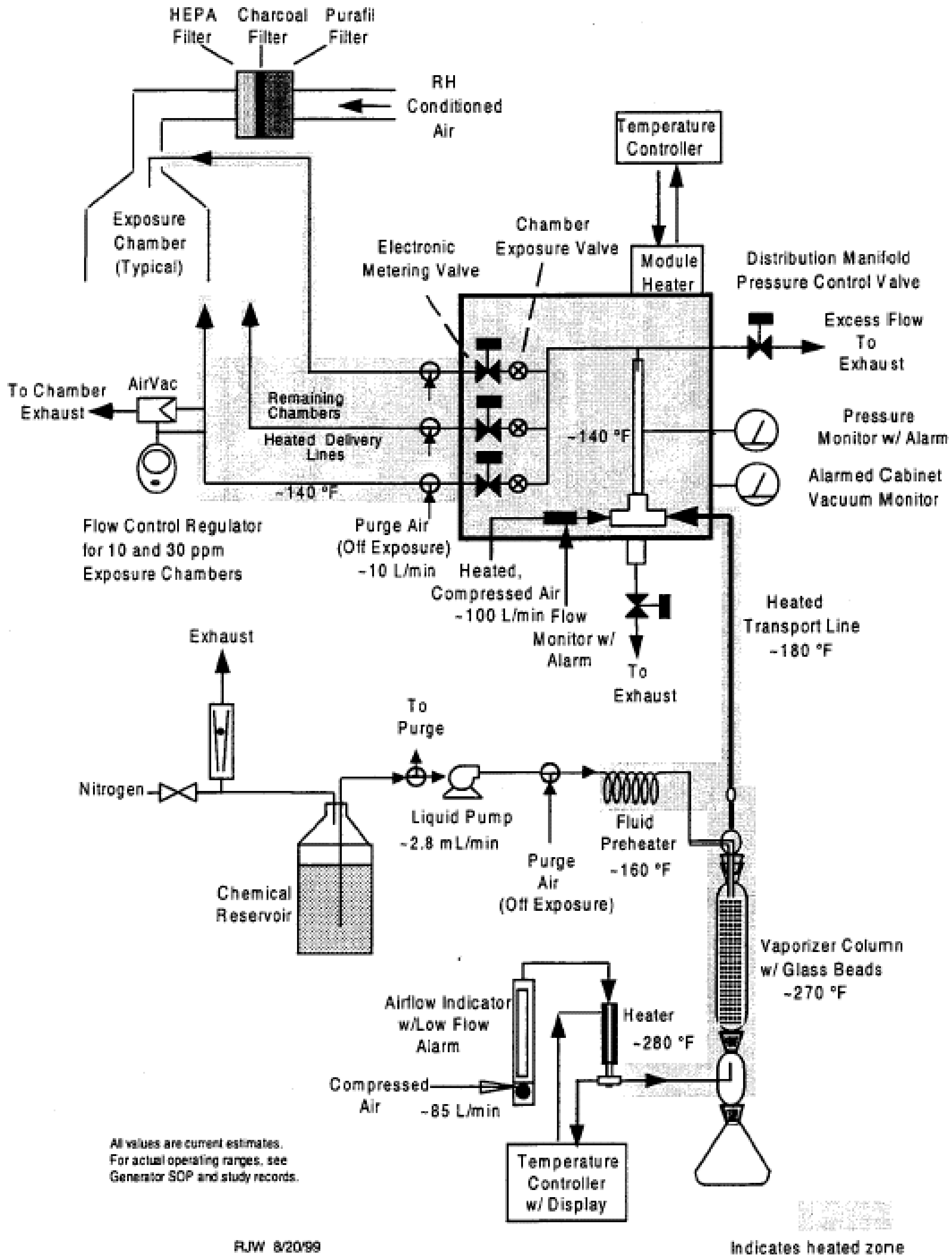

FIGURE I4
Schematic of the Vapor Generation and Delivery System in the Inhalation Studies of Divinylbenzene-HP

Table I2
Summary of Chamber Concentrations in the 2-Week Inhalation Studies of Divinylbenzene-HP

	Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers			
	25	94	25.0 ± 0.9
	50	101	51.2 ± 1.8
	100	96	99.3 ± 3.6
	200	98	205 ± 8.7
	400	106	400 ± 12
Mouse Chambers			
	25	102	25.0 ± 0.9
	50	110	51.1 ± 1.8
	100	105	99.1 ± 3.5
	200	107	206 ± 8.5
	400	9	390 ± 20

[a] Mean ± standard deviation

Table I3
Summary of Chamber Concentrations in the 3-Month Inhalation Studies of Divinylbenzene-HP

	Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers			
	25	607	25.1 ± 1.4
	50	581	50.5 ± 2.5
	100	571	99.5 ± 4.3
	200	576	204 ± 5.8
	400	578	405 ± 11
Mouse Chambers			
	12.5	628	12.5 ± 0.6
	25	627	25.0 ± 1.4
	50	600	50.4 ± 2.5
	100	589	99.6 ± 4.3
	200	594	204 ± 5.8

[a] Mean ± standard deviation

TABLE I4
Summary of Chamber Concentrations in the 2-Year Inhalation Studies of Divinylbenzene-HP

	Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers			
	100	4,416	100 ± 4
	200	4,428	200 ± 7
	400	4,463	403 ± 15
Mouse Chambers			
	10	4,528	10.0 ± 0.4
	30	4,733	30.1 ± 1.4
	100	4,856	99.9 ± 4.7

[a] Mean ± standard deviation

APPENDIX J
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NTP-2000 RAT AND MOUSE RATION

TABLE J1 Ingredients of NTP-2000 Rat and Mouse Ration J-2
TABLE J2 Vitamins and Minerals in NTP-2000 Rat and Mouse Ration J-2
TABLE J3 Nutrient Composition of NTP-2000 Rat and Mouse Ration J-3
TABLE J4 Contaminant Levels in NTP-2000 Rat and Mouse Ration J-4

TABLE J1
Ingredients of NTP-2000 Rat and Mouse Ration

Ingredients	Percent by Weight
Ground hard winter wheat	22.26
Ground #2 yellow shelled corn	22.18
Wheat middlings	15.0
Oat hulls	8.5
Alfalfa meal (dehydrated, 17% protein)	7.5
Purified cellulose	5.5
Soybean meal (49% protein)	5.0
Fish meal (60% protein)	4.0
Corn oil (without preservatives)	3.0
Soy oil (without preservatives)	3.0
Dried brewer's yeast	1.0
Calcium carbonate (USP)	0.9
Vitamin premix[a]	0.5
Mineral premix[b]	0.5
Calcium phosphate, dibasic (USP)	0.4
Sodium chloride	0.3
Choline chloride (70% choline)	0.26
Methionine	0.2

[a] Wheat middlings as carrier
[b] Calcium carbonate as carrier

TABLE J2
Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	4,000 IU	Stabilized vitamin A palmitate or acetate
D	1,000 IU	D-activated animal sterol
K	1.0 mg	Menadione sodium bisulfite complex
α-Tocopheryl acetate	100 IU	
Niacin	23 mg	
Folic acid	1.1 mg	
d-Pantothenic acid	10 mg	*d*-Calcium pantothenate
Riboflavin	3.3 mg	
Thiamine	4 mg	Thiamine mononitrate
B_{12}	52 µg	
Pyridoxine	6.3 mg	Pyridoxine hydrochloride
Biotin	0.2 mg	*d*-Biotin
Minerals		
Magnesium	514 mg	Magnesium oxide
Iron	35 mg	Iron sulfate
Zinc	12 mg	Zinc oxide
Manganese	10 mg	Manganese oxide
Copper	2.0 mg	Copper sulfate
Iodine	0.2 mg	Calcium iodate
Chromium	0.2 mg	Chromium acetate

[a] Per kg of finished product

Table J3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	13.9 ± 0.57	13.1 – 15.5	25
Crude fat (% by weight)	8.1 ± 0.24	7.6 – 8.5	25
Crude fiber (% by weight)	9.1 ± 0.57	8.0 – 10.5	25
Ash (% by weight)	5.1 ± 0.24	4.7 – 5.7	25
Amino Acids (% of total diet)			
Arginine	0.748 ± 0.053	0.670 – 0.850	12
Cystine	0.223 ± 0.027	0.150 – 0.250	12
Glycine	0.702 ± 0.043	0.620 – 0.750	12
Histidine	0.343 ± 0.023	0.310 – 0.390	12
Isoleucine	0.534 ± 0.041	0.430 – 0.590	12
Leucine	1.078 ± 0.059	0.960 – 1.140	12
Lysine	0.729 ± 0.065	0.620 – 0.830	12
Methionine	0.396 ± 0.053	0.260 – 0.460	12
Phenylalanine	0.611 ± 0.038	0.540 – 0.660	12
Threonine	0.492 ± 0.045	0.430 – 0.590	12
Tryptophan	0.129 ± 0.016	0.110 – 0.160	12
Tyrosine	0.378 ± 0.054	0.280 – 0.460	12
Valine	0.658 ± 0.049	0.550 – 0.710	12
Essential Fatty Acids (% of total diet)			
Linoleic	3.89 ± 0.278	3.49 – 4.54	12
Linolenic	0.30 ± 0.038	0.21 – 0.35	12
Vitamins			
Vitamin A (IU/kg)	4,943 ± 829	3,460 – 6,810	25
Vitamin D (IU/kg)	1,000[a]		
α-Tocopherol (ppm)	84.3 ± 17.06	52.0 – 110.0	12
Thiamine (ppm)[b]	7.5 ± 0.89	6.3 – 9.2	25
Riboflavin (ppm)	6.4 ± 2.11	4.20 – 11.20	12
Niacin (ppm)	78.6 ± 10.86	66.4 – 98.2	12
Pantothenic acid (ppm)	23.1 ± 3.61	17.4 – 29.1	12
Pyridoxine (ppm)[b]	8.88 ± 2.05	6.4 – 12.4	12
Folic acid (ppm)	1.84 ± 0.56	1.26 – 3.27	12
Biotin (ppm)	0.337 ± 0.13	0.225 – 0.704	12
Vitamin B_{12} (ppb)	64.8 ± 50.9	18.3 – 174.0	12
Choline (ppm)[b]	3,094 ± 292	2,700 – 3,790	12
Minerals			
Calcium (%)	1.036 ± 0.042	0.964 – 1.140	25
Phosphorus (%)	0.592 ± 0.034	0.517 – 0.667	25
Potassium (%)	0.668 ± 0.023	0.627 – 0.694	12
Chloride (%)	0.368 ± 0.033	0.300 – 0.423	12
Sodium (%)	0.189 ± 0.016	0.160 – 0.212	12
Magnesium (%)	0.200 ± 0.009	0.185 – 0.217	12
Sulfur (%)	0.176 ± 0.026	0.116 – 0.209	12
Iron (ppm)	177 ± 46.2	135 – 311	12
Manganese (ppm)	53.4 ± 6.42	42.1 – 63.1	12
Zinc (ppm)	52.5 ± 6.95	43.3 – 66.0	12
Copper (ppm)	6.64 ± 1.283	5.08 – 9.92	12
Iodine (ppm)	0.535 ± 0.242	0.233 – 0.972	12
Chromium (ppm)	0.545 ± 0.125	0.330 – 0.751	12
Cobalt (ppm)	0.23 ± 0.041	0.20 – 0.30	12

[a] From formulation
[b] As hydrochloride (thiamine and pyridoxine) or chloride (choline)

Table J4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.20 ± 0.052	0.10 – 0.37	25
Cadmium (ppm)	0.04 ± 0.007	0.04 – 0.07	25
Lead (ppm)	0.10 ± 0.100	0.05 – 0.54	25
Mercury (ppm)	<0.02		25
Selenium (ppm)	0.20 ± 0.043	0.14 – 0.28	25
Aflatoxins (ppb)	<5.00		25
Nitrate nitrogen (ppm)[c]	10.8 ± 3.28	6.85 – 21.1	25
Nitrite nitrogen (ppm)[c]	<0.61		25
BHA (ppm)[d]	<1.0		25
BHT (ppm)[d]	<1.0		25
Aerobic plate count (CFU/g)	12.0 ± 6	10.0 – 40.0	25
Coliform (MPN/g)	2.0 ± 1.8	0.0 – 3.6	25
Escherichia coli (MPN/g)	<10		25
Salmonella (MPN/g)	Negative		25
Total nitrosoamines (ppb)[e]	4.6 ± 1.22	2.3 – 7.8	25
N-Nitrosodimethylamine (ppb)[e]	1.9 ± 0.53	1.0 – 2.9	25
N-Nitrosopyrrolidine (ppb)[e]	2.7 ± 0.95	1.1 – 5.1	25
Pesticides (ppm)			
α-BHC	<0.01		25
β-BHC	<0.02		25
γ-BHC	<0.01		25
δ-BHC	<0.01		25
Heptachlor	<0.01		25
Aldrin	<0.01		25
Heptachlor epoxide	<0.01		25
DDE	<0.01		25
DDD	<0.01		25
DDT	<0.01		25
HCB	<0.01		25
Mirex	<0.01		25
Methoxychlor	<0.05		25
Dieldrin	<0.01		25
Endrin	<0.01		25
Telodrin	<0.01		25
Chlordane	<0.05		25
Toxaphene	<0.10		25
Estimated PCBs	<0.20		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.10		25
Methyl chlorpyrifos	0.180 ± 0.103	0.047 – 0.499	25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion	0.207 ± 0.151	0.020 – 0.557	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

[a] All samples were irradiated. CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] All values were corrected for percent recovery.

APPENDIX K
SENTINEL ANIMAL PROGRAM

METHODS K-2
RESULTS K-4

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from five male and five female chamber control rats and mice at the end of the 2-week and 3-month studies. During the 2-year studies, samples were collected from five male and five female sentinel rats and mice at 6, 12, and 18 months and from five male and five female 400 ppm rats and five male and five female 100 ppm mice at the end of the studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and analyzed at the study laboratory or sent to MA Bioservices, Inc. (Rockville, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
2-Week Study	
ELISA	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	Study termination
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	Study termination
Sendai	Study termination
3-Month Study	
ELISA	
PVM	Study termination
RCV/SDA	Study termination
Sendai	Study termination
Immunofluorescence Assay	
Parvovirus	Study termination

Method and Test	Time of Analysis
RATS (continued)	
2-Year Study	
ELISA	
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
RCV/SDA	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
Parvovirus	6, 12, and 18 months, study termination
MICE	
2-Week Study	
ELISA	
GDVII (mouse encephalomyelitis virus)	Study termination
MVM (minute virus of mice)	Study termination
MHV (mouse hepatitis virus)	Study termination
M. pulmonis	Study termination
PVM	Study termination
Sendai	Study termination
3-Month Study	
ELISA	
Ectromelia virus	Study termination
EDIM (epizootic diarrhea of infant mice)	Study termination
GDVII	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
MVM	Study termination
Mouse adenoma virus-FL	Study termination
MHV	Study termination
M. pulmonis	Study termination
PVM	Study termination
Reovirus	Study termination
Sendai	Study termination
Immunfluorescence Assay	
Parvovirus	Study termination

Method and Test	Time of Analysis
MICE (continued)	
2-Year Study	
ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM	6, 12, and 18 months, study termination
GDVII	6, 12, and 18 months, study termination
LCM	6, 12, and 18 months, study termination
Mouse adenoma virus	6, 12, and 18 months, study termination
MCMV (mouse cytomegalovirus)	Study termination
MHV	6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
Parvovirus	6, 12, and 18 months, study termination

RESULTS

All test results were negative.

APPENDIX L
PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL

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PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL

INTRODUCTION

A physiologically based pharmacokinetic (PBPK) model was developed to describe the uptake, distribution, and metabolism of *meta*-divinylbenzene (*m*-divinylbenzene) in rats. This PBPK model was based on previously published models for styrene (Ramsey and Anderson, 1984; Csanady, *et al*., 1994) due to similarity in the chemical structures of styrene (C_8H_8) and *m*-divinylbenzene ($C_{10}H_{10}$) and the presumed likeness of their metabolic pathways. The model is specific to male Fischer 344 rats. There were twelve parameters that did not have literature estimates. These parameters were estimated by fitting model predictions to data from NTP toxicokinetic studies (Slauter and Jeffcoat, 1991).

MODEL DEVELOPMENT

The PBPK model (Figure L1) has separate compartments representing adipose, kidney, liver, lung, rapidly perfused and slowly perfused tissues, venous blood, and arterial blood. All of the tissue compartments are modeled as flow limited. There is also a compartment representing the gut. The gut compartment represents the gastrointestinal lumen and is not a compartment with blood flow. There is a submodel for *m*-divinylbenzene as well as a submodel representing the first metabolite of *m*-divinylbenzene. Urinary clearance is modeled as a linear process from the kidney for both *m*-divinylbenzene and the *m*-divinylbenzene metabolite. Oral doses start in the gut compartment. Uptake from the gut to the liver and elimination from the gut to the feces are also modeled as linear processes. Biliary secretion of *m*-divinylbenzene is reported to follow Michaelis-Menten kinetics (Slauter and Jeffcoat, 1991) and enterohepatic recirculation is possible in the model. Biliary secretion, gut uptake, and fecal elimination are included for both *m*-divinylbenzene and *m*-divinylbenzene metabolite. Metabolism of *m*-divinylbenzene takes place in the liver and is assumed to follow Michaelis-Menten kinetics. Metabolism is the only link between the *m*-divinylbenzene and *m*-divinylbenzene metabolite submodels. The maximum rates of metabolism and biliary secretion were scaled to body weight. Rapid venous and arterial equilibration was assumed for the blood. Intravenous dosing was described as an infusion directly into the blood. The model accounts for exhaled test chemical.

The physiological parameters for rats shown in Table L1 were taken from the literature (Brown *et al.*, 1997). In order to account for reabsorption of chemical released by exhaled breath, a linear factor, k_{resorp} was incorporated into the model. To calculate the partition coefficients for *m*-divinylbenzene, we used the relationship:

$$\frac{\log K_{ow}\, mDVB}{\log K_{ow}\, (styrene)} = \frac{P_{i,\ mDVB}}{P_{i,\ styrene}}$$

where, K_{ow} represents the octanol:water partition coefficient and $P_{i,mDVB}$ represents the tissue:blood partition coefficient for *m*-divinylbenzene and tissue compartment *i*. The online version of the program KowWin (SRC, 2004) was used to estimate the octanol:water partition coefficients of *m*-divinylbenzene and styrene (Meylan and Howard, 1995). The partition coefficients associated with the *m*-divinylbenzene metabolite group were taken to be the same as those for the main styrene metabolite, styrene oxide (Table L2). The single-dose toxicokinetic data from the NTP studies used for parameter estimation included tissue concentrations (blood, fat, kidney, liver, and muscle) and amounts eliminated in exhaled breath, urine, and feces (Slauter and Jeffcoat, 1991). In these studies, male Fisher 344 rats were given a single intravenous injection of 40 mg [^{14}C]-*m*-divinylbenzene/kg body weight or a single gavage dose of 40, 400, or 1,200 mg/kg. Experimental samples were collected up to 72 hours after dosing. In addition, a bile secretion study was conducted. All data are total radioactivity, and there were no known levels of quantification issues.

There were twelve unknown parameters in the model with very little information to suggest the correct order of magnitude for any of them. Therefore, the values of the parameters were first found using a differential evolution optimization algorithm (ICSI, 1995). The advantage of this type of algorithm is that it has the ability to search across the global parameter space without being restricted to a local minimum. The cost function computes the sum of squared errors between the simulated results and experimental measurements for bile, volatile breath, urine, feces, blood, fat, kidney, and liver. Another cost function which computed the natural logarithm of the sum of squared errors was also examined, however, the results obtained from each cost function were similar. The differential evolution algorithm was run for at least 1,000 generations. The best parameters from the differential evolution algorithm were then used as the initial conditions in the constrained optimization routine in MATLAB® (The Math Works, Inc., Natick, MA) to find the final parameter values (Table L3).

Definitions of Abbreviations

$A_{i,j}$ = Amount of *m*-divinylbenzene (j = *m*-divinylbenzene) or *m*-divinylbenzene metabolite($j = m$) in compartment i (mg)
V_i = Volume of compartment i (L)
$C_{i,j}$ = Concentration of chemical j in compartment i (mg/L)
Q_i = Blood flow rate in compartment i (L/hour)
$P_{i,j}$ = Tissue$_i$:blood partition coefficient for chemical j (unitless)
$Vmax\_bile_j$ = Maximum biliary excretion rate for chemical j (mg/L per hour)
Km_bile_j = Michaelis-Menten constant associated with bile excretion of chemical j (mg/L)
k_urine_j = Urinary elimination rate constant for chemical j (hour^{-1})
k_uptake_j = Gastrointestinal lumen absorption rate constant for chemical j (hour^{-1})
k_feces_j = Fecal elimination rate constant for chemical j (hour^{-1})
$Vmax$ = Maximum metabolism rate (mg/L per hour)
Km = Michaelis-Menten constant associated with metabolism (mg/L)
met = metabolized
uptake = chemical absorption from gastrointestinal lumen to liver

Model Equations

Equations for typical flow-limited tissue:

$$\frac{dA_{tissue,j}}{dt} = Q_{tissue} * \left(C_{arterial,j} - \frac{C_{tissue,j}}{P_{tissue,j}} \right)$$

$$\frac{dA_{urine,j}}{dt} = k\_urine_j * \frac{A_{kidney,j}}{P_{kidney,j}}$$

$$\frac{dA_{kidney,j}}{dt} = Q_{kidney} * \left(C_{arterial,j} - \frac{C_{kidney,j}}{P_{kidney,j}} \right) - \frac{dA_{urine,j}}{dt}$$

$$\frac{dA_{bile,j}}{dt} = \frac{Vmax\_bile_j * \dfrac{C_{liver,j}}{P_{liver,j}}}{Km\_bile_j + \dfrac{C_{liver,j}}{P_{liver,j}}}$$

$$\frac{dA_{uptake,j}}{dt} = k\_uptake_j * A_{gut,j}$$

$$\frac{dA_{feces,j}}{dt} = k\_feces_j * A_{gut,j}$$

$$\frac{dA_{gut,j}}{dt} = \frac{dA_{bile,j}}{dt} - \frac{dA_{uptake,j}}{dt} - \frac{dA_{feces,j}}{dt}, where \quad A_{gut,mDVB}(0) = dose_{oral,mDVB}$$

$$\frac{dA_{met,mDVB}}{dt} = \frac{Vmax * \dfrac{C_{liver,mDVB}}{P_{liver,mDVB}}}{Km + \dfrac{C_{liver,mDVB}}{P_{liver,mDVB}}}$$

$$\frac{dA_{liver,mDVB}}{dt} = Q_{liver} * \left(C_{arterial,mDVB} - \frac{C_{liver,mDVB}}{P_{liver,mDVB}} \right) - \frac{dA_{met,mDVB}}{dt} - \frac{dA_{bile,mDVB}}{dt} + \frac{dA_{uptake,mDVB}}{dt}$$

$$\frac{dA_{liver,m}}{dt} = Q_{liver} * \left(C_{arterial,m} - \frac{C_{liver,m}}{P_{liver,m}} \right) + \frac{dA_{met,mDVB}}{dt} - \frac{dA_{bile,m}}{dt} + \frac{dA_{uptake,m}}{dt}$$

$$C_{venous,mDVB} = \frac{\left(dose_{IV,mDVB} + \sum Q_i * \dfrac{C_{i,mDVB}}{P_{i,mDVB}} \right)}{Q_{cardiac}}$$

$$C_{venous,m} = \frac{\sum Q_i * \frac{C_{i,m}}{P_{i,m}}}{Q_{cardiac}}$$

$$C_{arterial,j} = \frac{Q_{alveolar} * C_{inhaled,j} + Q_{cardiac} * C_{venous,j}}{Q_{cardiac} + \frac{Q_{alveolar,j}}{P_{air,j}}}$$

$$\frac{dA_{exhaled,j}}{dt} = k_{resorp} * Q_{alveolar} * \frac{C_{arterial,j}}{P_{air,j}}$$

$$C_{i,j} = \frac{A_{i,j}}{V_{i,j}}$$

RESULTS

The results of simulations performed with the PBPK model for *m*-divinylbenzene compared to the experimental data from the NTP toxicokinetic studies are shown in Figures L2 to L12. Note that the model tracks amounts of *m*-divinylbenzene and *m*-divinylbenzene metabolite separately. The available toxicokinetic data, however, were for dosing radiolabeled *m*-divinylbenzene; all of the data are thus for total radiolabel and there is no differentiation in the experimental data between *m*-divinylbenzene and its metabolites.

For each of the four doses used, there is a figure containing five plots illustrating the concentrations of *m*-divinylbenzene equivalents in adipose, venous blood, liver, muscle, and kidney (Figures L5, L7, L10, and L12). All of these tissues, with the exception of muscle, correspond directly with compartments in the PBPK model. For muscle data, the plots are the simulated results from the slowly perfused tissue compartment; muscle is the primary component of the slowly perfused compartment. Oftentimes the model slightly overpredicts the data in this case, which may be explained by the fact that the slowly perfused tissue compartment, while including muscle, is composed of other tissues grouped together as well.

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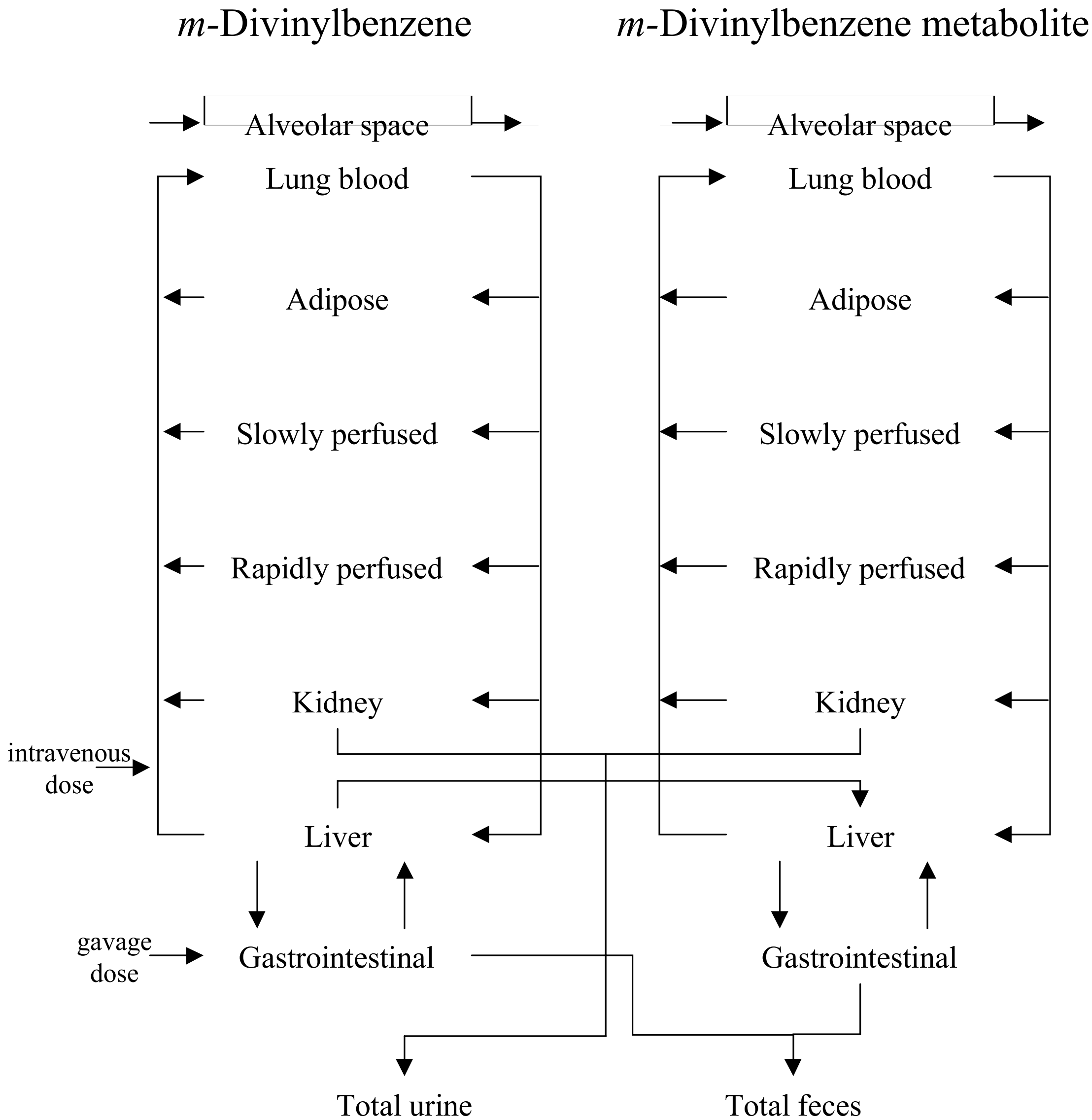

FIGURE L1
Physiologically Based Pharmacokinetic Model for Rats Exposed to [^{14}C]-*m*-Divinylbenzene by Single-Dose Intravenous Injection or Oral Gavage

Table L1
Physiological Parameters of Rats for the Physiologically Based Pharmacokinetic Model of *m*-Divinylbenzene[a]

	Value
Parameter	
Body weight (kg)	0.2686
Cardiac output (L/hour per kg $^{0.75}$ body weight)	14.1
Alveolar ventilation (L/hour per kg $^{0.75}$ body weight)	22.0
Reabsorption factor (unitless)	0.3
Tissue Volume as Fraction of Body Weight	
Fat	0.09
Gut	0.03
Kidney	0.007
Liver	0.04
Rapidly perfused tissue	0.153
Slowly perfused tissue	0.53
Tissue Blood Flow as Fraction of Cardiac Output	
Fat	0.07
Kidney	0.141
Liver	0.183
Rapidly perfused tissue	0.266
Slowly perfused tissue	0.34

[a] Parameter estimates were derived from Brown *et al*. (1997).

Table L2
Partition Coefficients for *m*-Divinylbenzene and *m*-Divinylbenzene Metabolite for the Physiologically Based Pharmacokinetic Model of *m*-Divinylbenzene[a]

Tissue	Partition Coefficients for *m*-Divinylbenzene	Partition Coefficients for *m*-Divinylbenzene Metabolite
Fat	53.779	6.1
Kidney	1.499	2.6
Liver	1.552	2.6
Rapidly perfused tissues	1.499	2.6
Slowly perfused tissues	1.131	1.5
Air	144.6	10,000.

[a] All coefficients, except air are expressed as tissue:blood ratios; air is blood:air ratio. Values were calculated from octanol:water partition coefficients obtained from Meylan and Howard (1995) and SRC (2004).

Table L3
Parameter Estimates for Rats from the Physiologically Based Pharmacokinetic Model of *m*-Divinylbenzene

Parameter	Value
V_{max} (mg/L per hour)	26.9403
K_m (mg/L)	1.0736
$V_{max}\_bile_{mDVB}$ (mg/L per hour)	10.5794
$K_m\_bile_{mDVB}$ (mg/L)	0.6742
k_urine_{mDVB} (hour $^{-1}$)	0.0605
k_uptake_{mDVB} (hour $^{-1}$)	0.0242
k_feces (hour $^{-1}$)	0.0069
$V_{max}\_bile_{met}$ (mg/L per hour)	0.1094
$k_m\_bile_{met}$ (mg/L)	0.0084
k_urine_{met} (hour $^{-1}$)	31.3985
k_uptake_{met} (hour $^{-1}$)	0.0015
k_feces_{met} (hour $^{-1}$)	0.0320

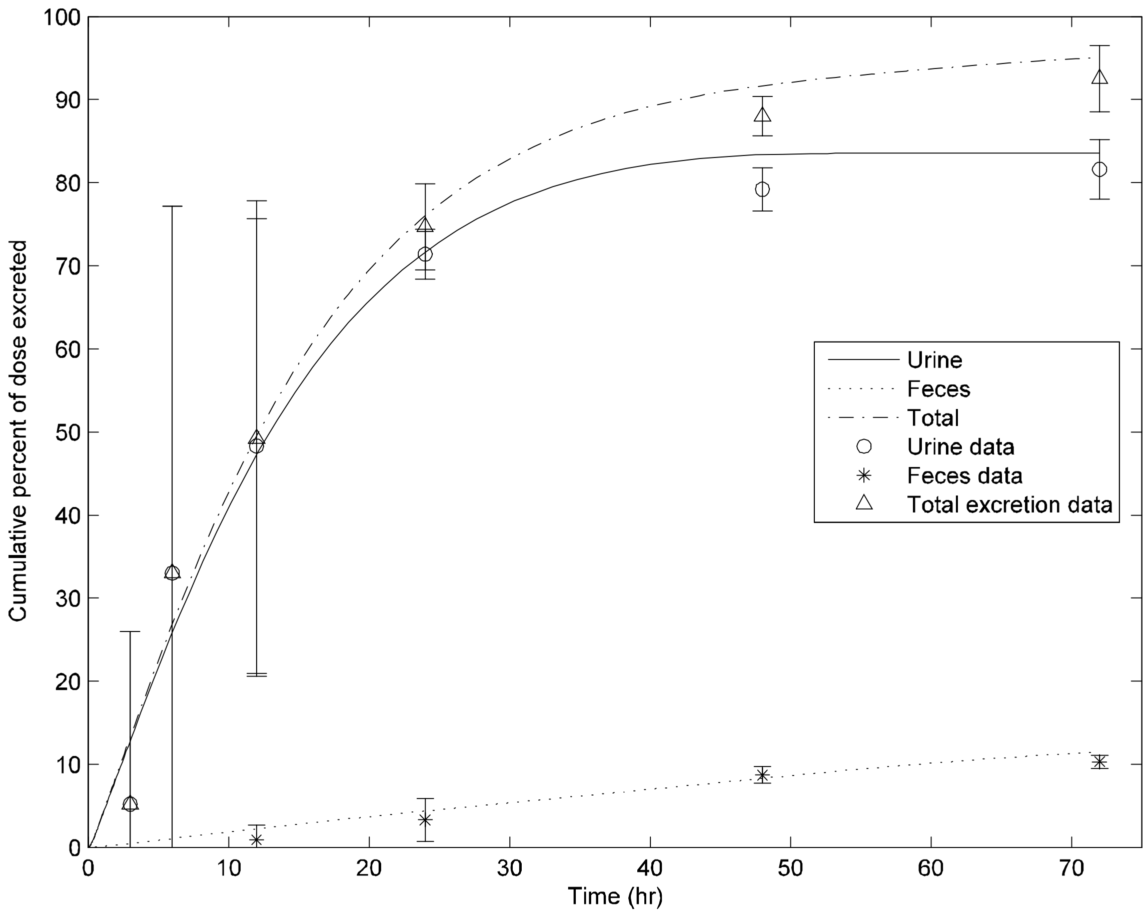

FIGURE L2
Excretion of Radiolabel in Urine and Feces of Rats After a Single Intravenous Injection of 40 mg/kg [^{14}C]-*m*-Divinylbenzene
Lines represent the predicted best-fit curve (from the PBPK model) plotted through the observed data points. Data points are represented as mean ± 2 standard deviations (n=4).

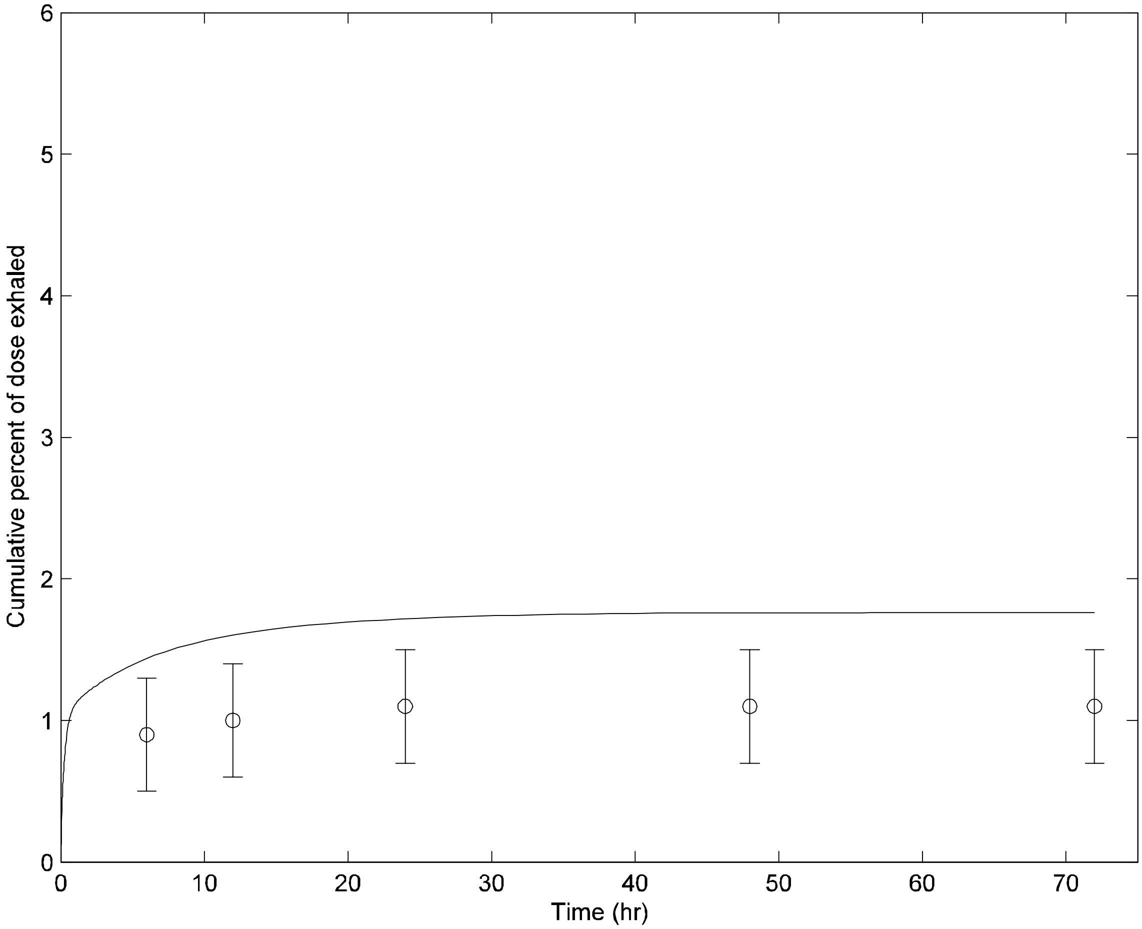

FIGURE L3
Exhalation of Radiolabel by Rats After a Single Intravenous Injection of 40 mg/kg [^{14}C]-*m*-Divinylbenzene
The solid line represents the predicted best-fit curve (from the PBPK model) plotted through the observed data points. Data points are represented as mean ± 2 standard deviations (n=4).

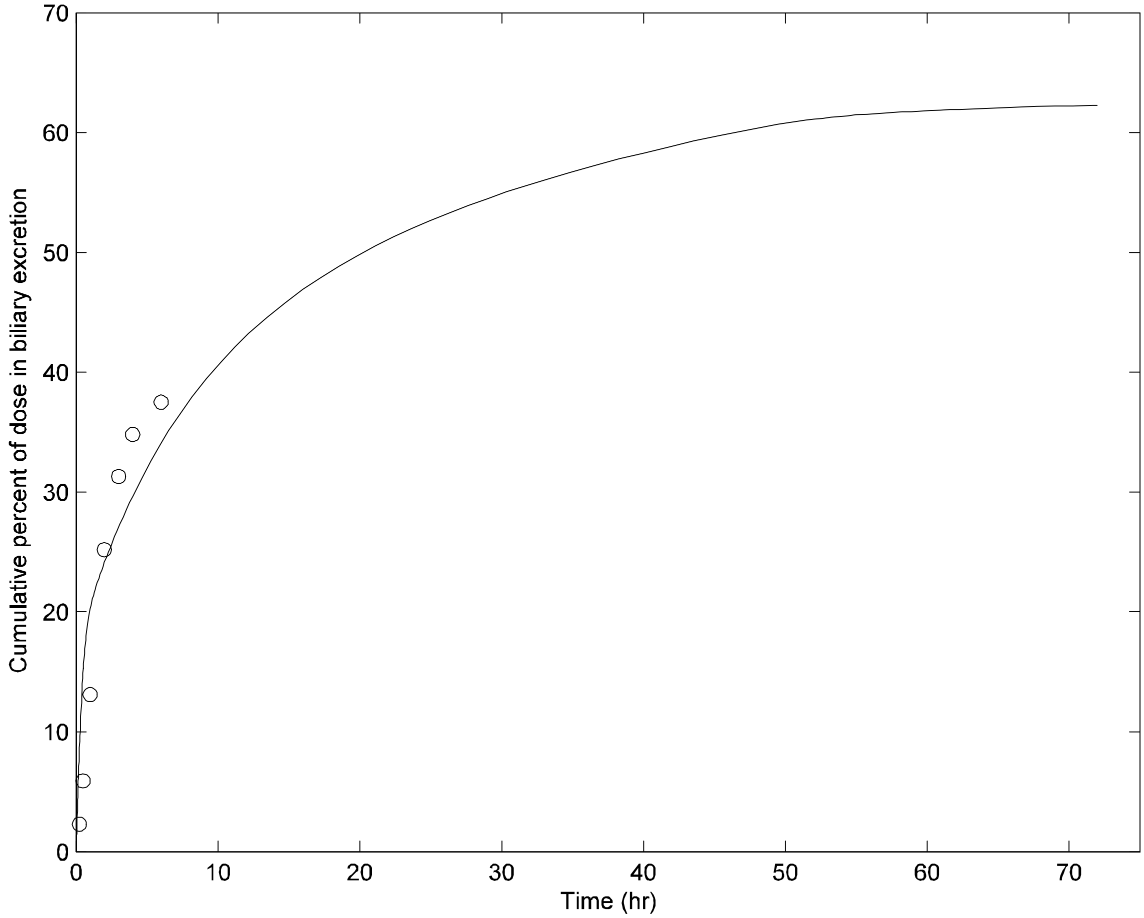

Figure L4
Excretion of Radiolabel in Bile of Rats After a Single Intravenous Injection of 40 mg/kg [^{14}C]-*m*-Divinylbenzene
The solid line represents the predicted best-fit curve (from the PBPK model) through the observed data points.

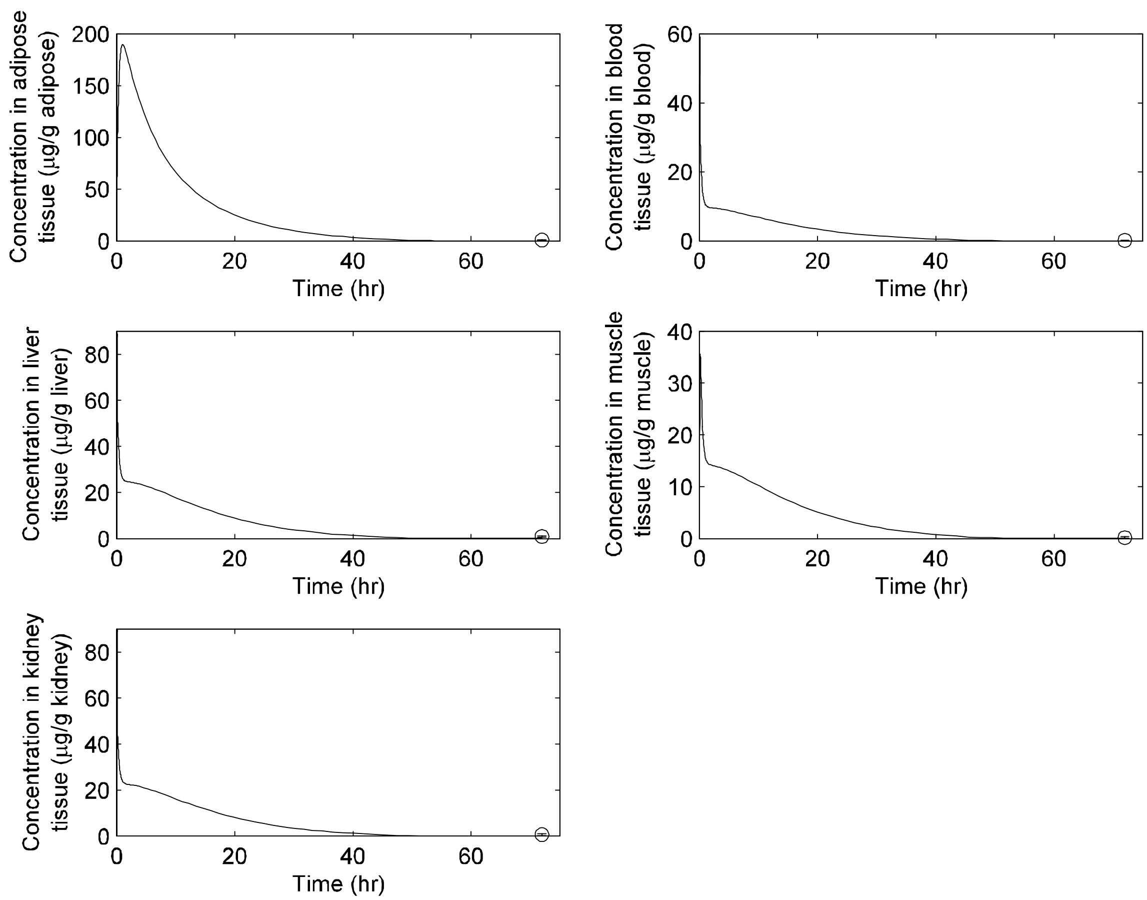

FIGURE L5
Tissue Concentrations of *m*-Divinylbenzene Equivalents in Rats
After a Single Intravenous Injection of 40 mg/kg [^{14}C]-*m*-Divinylbenzene
The solid line represents the predicted best-fit curve (from the PBPK model) through the observed data points. Data points are represented as mean ± 2 standard deviations (n=4).

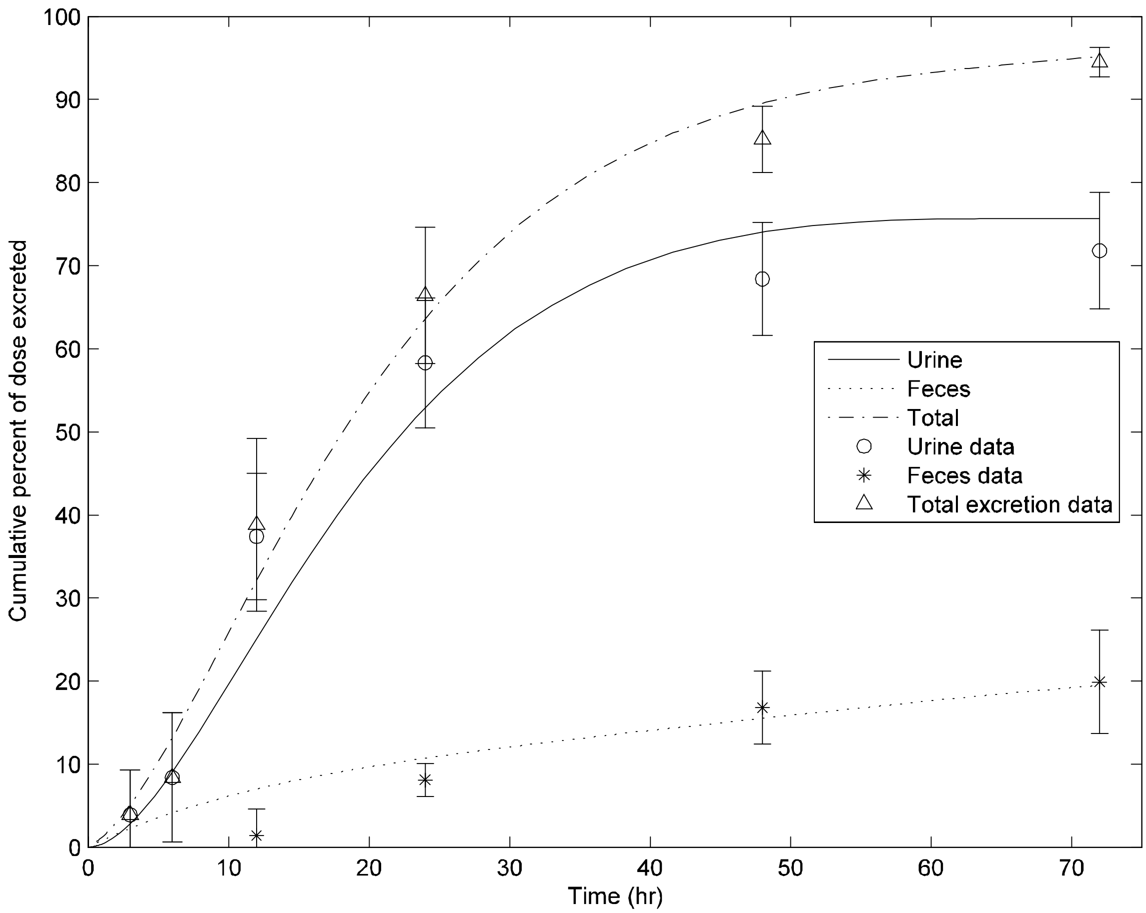

FIGURE L6
Excretion of Radiolabel in Urine and Feces of Rats After a Single Gavage Dose of 40 mg/kg [^{14}C]-*m*-Divinylbenzene
Lines represent the predicted best-fit curves (from the PBPK model) plotted through the observed data points. Data points are represented as mean ± 2 standard deviations (n=4).

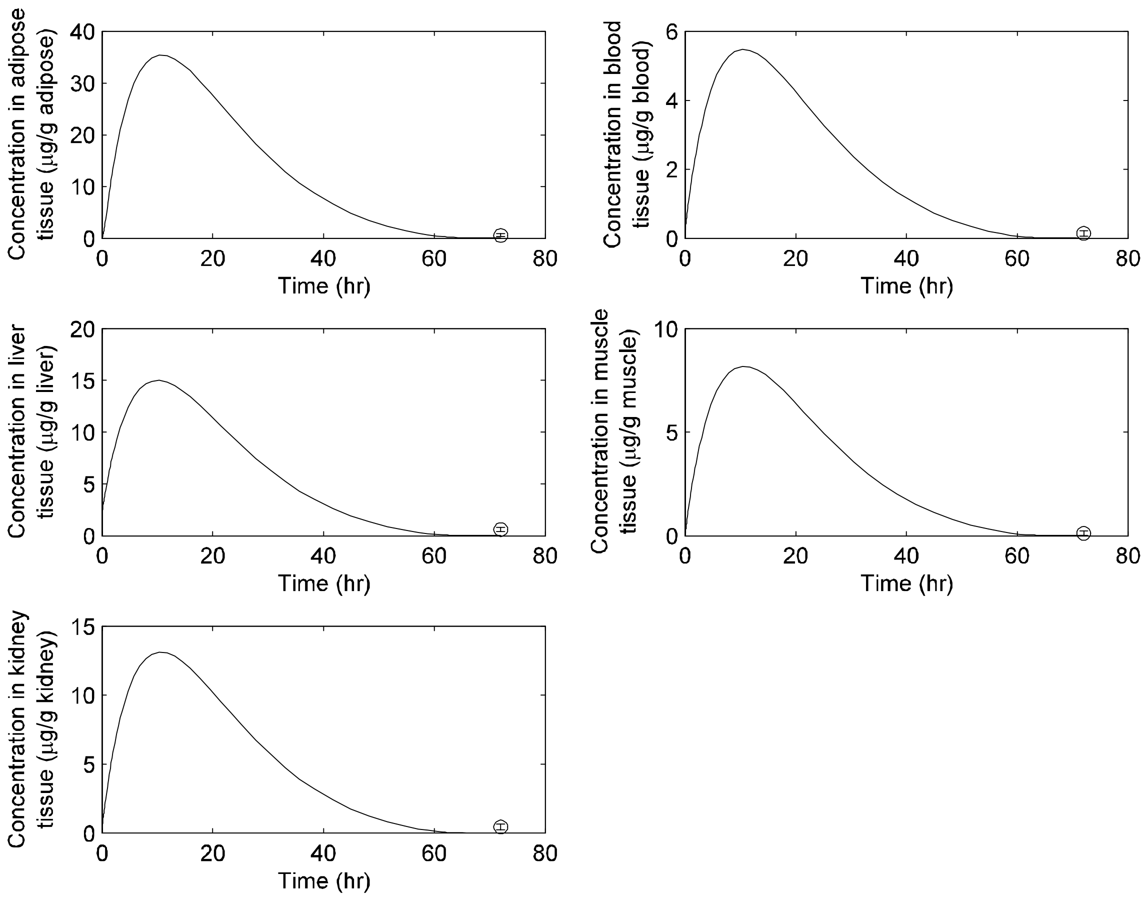

Figure L7

Tissue Concentrations of *m*-Divinylbenzene Equivalents in Rats After a Single Gavage Dose of 40 mg/kg [^{14}C]-*m*-Divinylbenzene

The solid lines represent the predicted best-fit curves (from the PBPK model) through the observed data points. Data points are represented as mean ± 2 standard deviations (n=4).

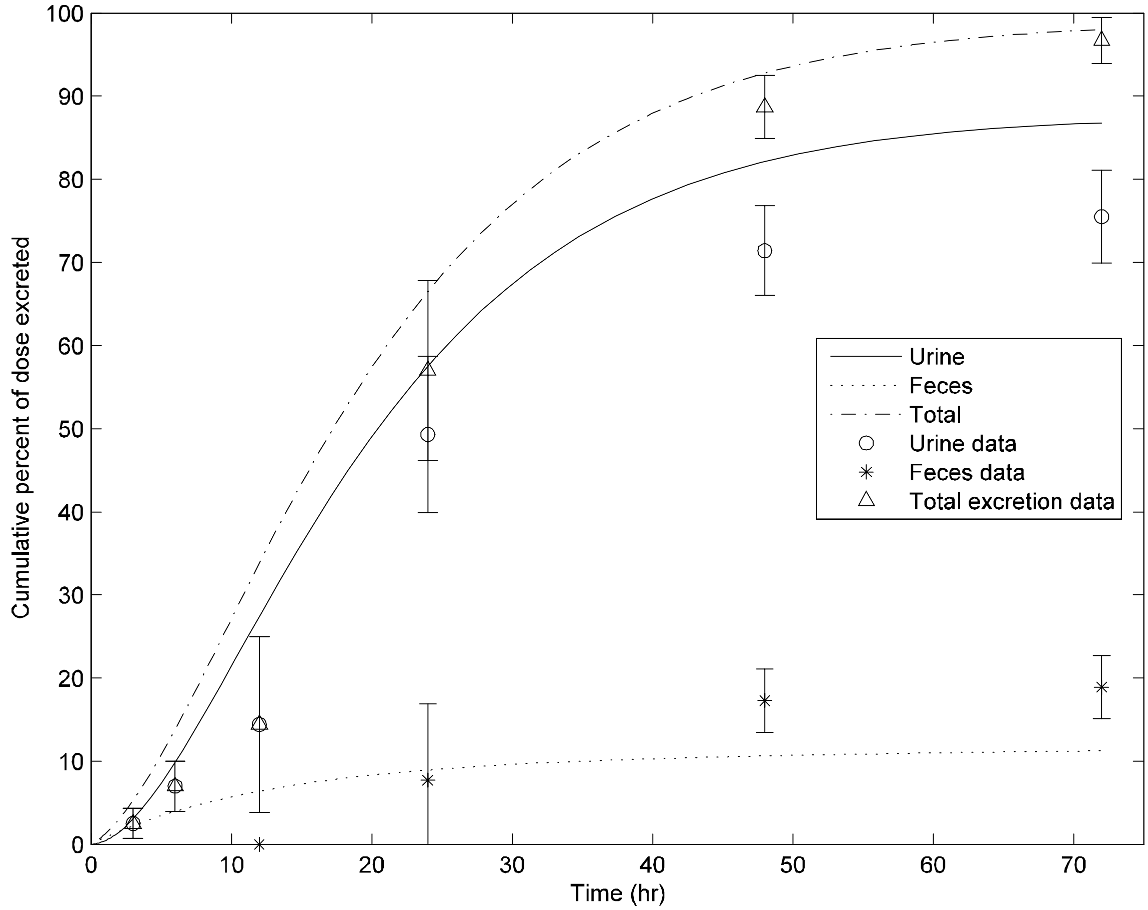

FIGURE L8
Excretion of Radiolabel in Urine and Feces of Rats After a Single Gavage Dose of 400 mg/kg [^{14}C]-*m*-Divinylbenzene
Lines represent the predicted best-fit curves (from the PBPK model) plotted through the observed data points. Data points are represented as mean ± 2 standard deviations (n=4).

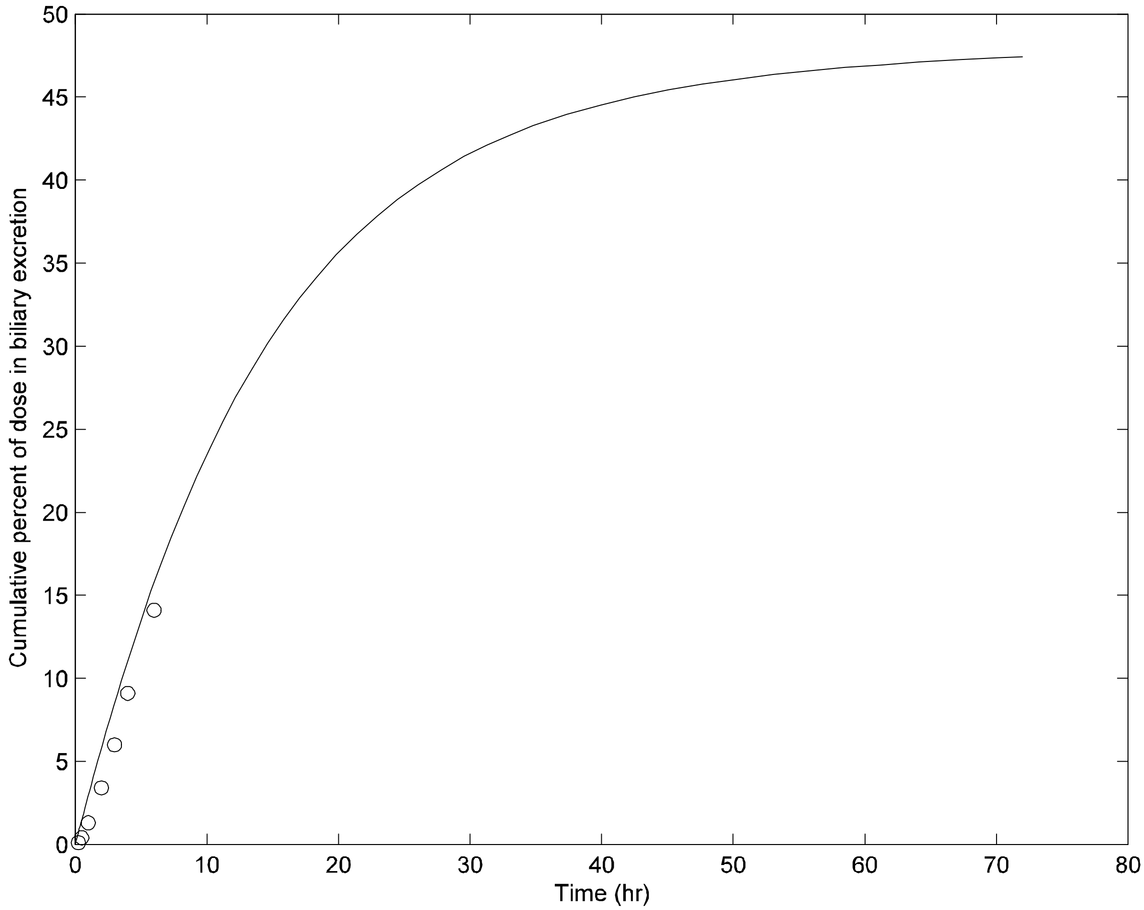

FIGURE L9
Excretion of Radiolabel in Bile of Rats After a Single Gavage Dose of 400 mg/kg [^{14}C]-*m*-Divinylbenzene
The solid line represents the predicted best-fit curve (from PBPK model) through the observed data points.

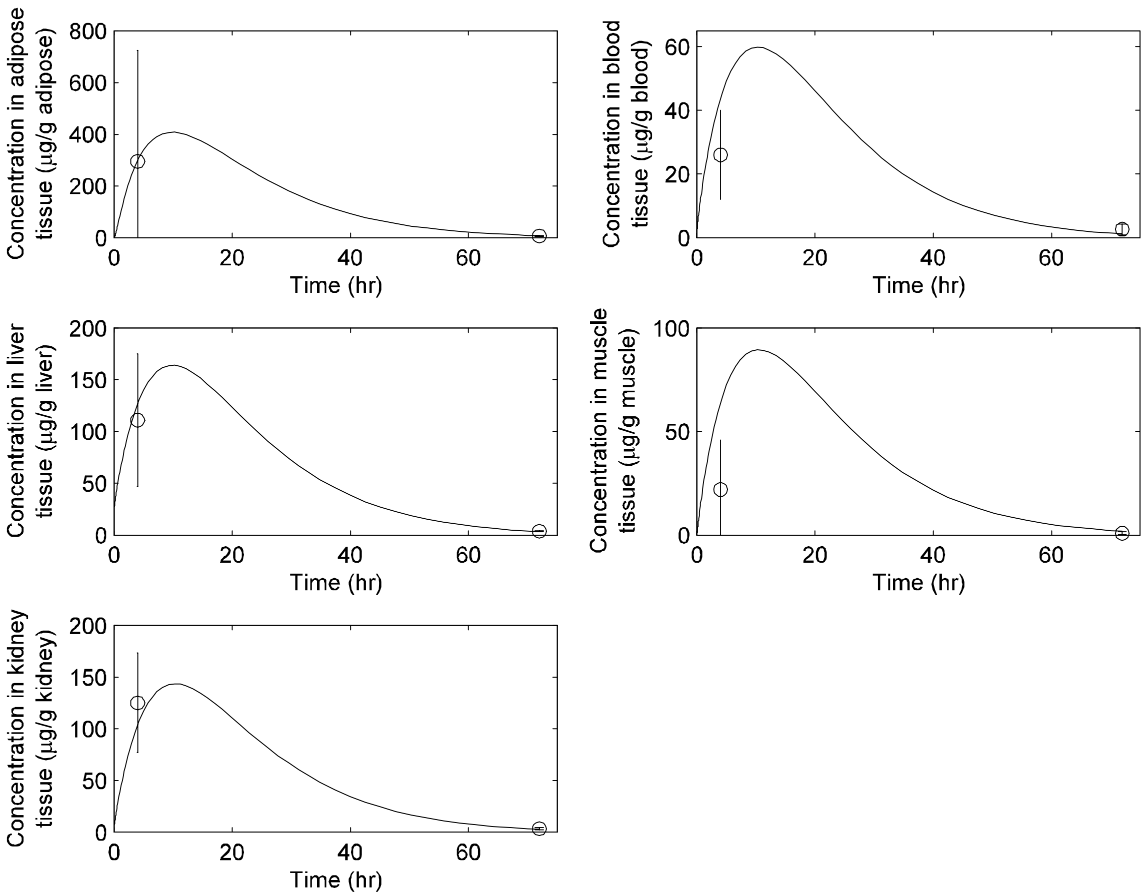

Figure L10
Tissue Concentrations of *m*-Divinylbenzene Equivalents in Rats After a Single Gavage Dose of 400 mg/kg [^{14}C]-*m*-Divinylbenzene
The solid lines represent the predicted best-fit curve (from the PBPK model) through the observed data points. Data points are represented as mean ± 2 standard deviations (n=4).

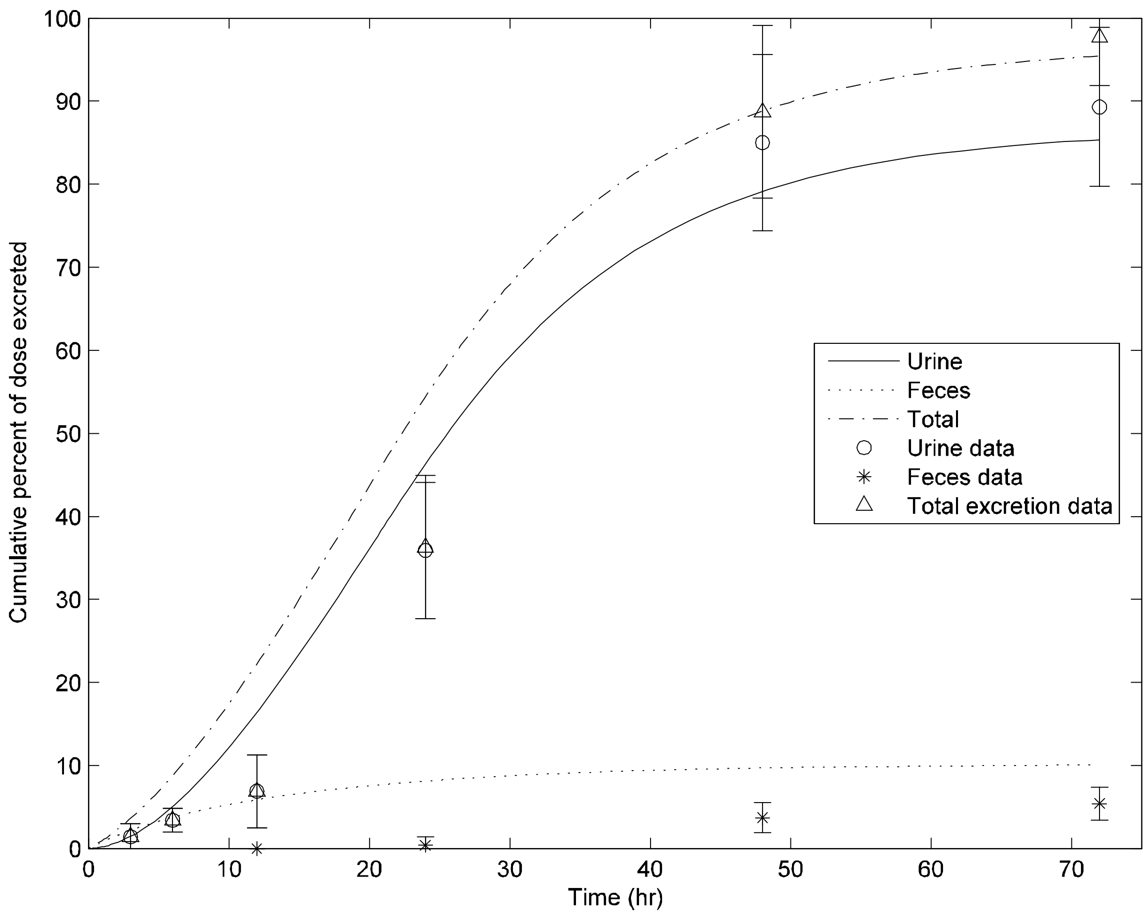

FIGURE L11
Excretion of Radiolabel in Urine and Feces of Rats After a Single Gavage Dose of 1,200 mg/kg [^{14}C]-*m*-Divinylbenzene
Lines represent the predicted best-fit curves (from the PBPK model) plotted through the observed data points. Data points are represented as mean ± 2 standard deviations (n=4).

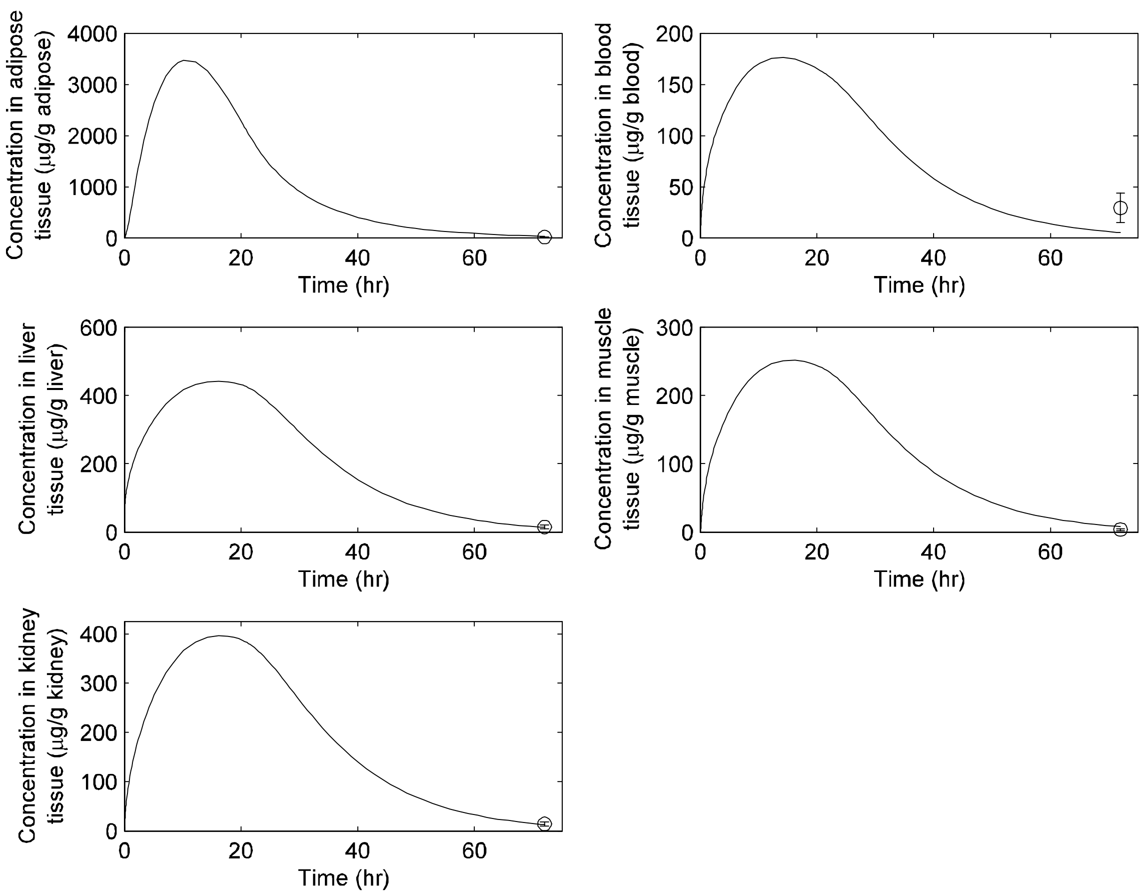

FIGURE L12
Tissue Concentrations of *m*-Divinylbenzene Equivalents in Rats After a Single Gavage Dose of 1,200 mg/kg [^{14}C]-*m*-Divinylbenzene
The solid lines represent the predicted best-fit curve (from the PBPK model) plotted through the observed data points. Data points are represented as mean ± 2 standard deviations (n=4).